Prediction Models for Pneumonia Among Children in the Emergency Department

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SUMMARY

We evaluated five previously published prediction models for radiographic pneumonia (Neuman, Oostenbrink, Lynch, Mahabee-Gittens, and Lipsett) using data from a single-center prospective study of patients 3 months to 18 years with signs of lower respiratory tract infection. Our outcome was radiographic pneumonia. We compared each model's area under the receiver operating characteristic curve (AUROC) and evaluated their diagnostic accuracy at statistically-derived cutpoints.

Radiographic pneumonia was identified in 253 (22.2%) of 1142 patients. When using model coefficients derived from the study dataset, AUROC ranged from 0.58 (95% confidence interval, 0.52-0.64) to 0.79 (95% confidence interval, 0.75-0.82). When using coefficients derived from original study models, two studies demonstrated an AUROC >0.70 (Neuman and Lipsett); this increased to three after deriving regression coefficients from the study cohort (Neuman, Lipsett, and Oostenbrink). Two models required historical and clinical data (Neuman and Lipsett), and the third additionally required C-reactive protein (Oostenbrink). At a statistically derived cutpoint of predicted risk from each model, sensitivity ranged from 51.2% to 70.4%, specificity 49.9% to 87.5%, positive predictive value 16.1% to 54.4%, and negative predictive value 83.9% to 90.7%.

Prediction models for radiographic pneumonia had varying performance. The three models with higher performance may facilitate clinical management by predicting the risk of radiographic pneumonia among children with lower respiratory tract infection.

COMMENTARIES

Evidence-based Medicine Viewpoint

Ramgopal, et al. [1] evaluated various models designed to predict the presence of radiographic pneumonia among children with clinical features of lower respiratory tract infection (LRTI) [1]. The justification was that this could reduce the tendency to perform chest *X*-rays, especially as radiography is not recommended in routine cases. Further, as clinicians tend to prescribe antibiotics to those with radiographic pneumonia, reducing the need for chest *X*-rays may indirectly reduce the indiscriminate use of antimicrobials also. The investigators evaluated the models, by conducting secondary data analysis of a study conducted by them, wherein children aged 3mo-18y with clinical criteria of LRTI undergoing chest *X*-rays for suspected pneumonia, were prospectively enrolled [2]. In the original study [2], they also developed a prediction model for radiographic pneumonia, and compared their own model to the external models.

Five prediction models published between 2004 and 2021 were evaluated [3-7]. Briefly, *X*-rays of the children in the prospective cohort [2] meeting the criteria in each of the prediction models, were independently examined by two qualified radiologists, who were blinded to the clinical information [1]. Their reporting determined the presence or absence of radiographic pneumonia, based on which the predictive capability of each of the models was determined. The investigators used two methods to analyze the data, first using the values (of regression coefficients) as published in the original studies, and second using their own dataset to estimate new regression coefficients for the variables in the models.

The main results are summarized in **Table 1**, along with calculations of the accuracy of each model at hypothetical prevalence of 10%, 20% and 40% radio-graphic pneumonia. Firstly, none of the five prediction models reliably predicts the presence or absence of radiographic pneumonia. Second, there are wide variations in the performance of the models. Third, the specificity of the five models improved when the regression coefficients of the investigators' dataset [1] were used. An older systematic review [8] evaluating the prediction of radio-graphic pneumonia from clinical symptoms and signs, also identified only moderate sensitivity and specificity.

Critical Appraisal

The study methods broadly met the standards expected for

Table 1: Summary of the Study Results With Estimates of Accuracy Using Hypothetical Prevalences of Radiographic Pneumonia

	Data analysis using regression coefficients as published in the original studies				*Accuracy at an estimated prevalence of:*			*Data analysis using regression coefficients derived for the prospective study*				*Accuracy at an estimated prevalence of:*		
	Sn	Sp	LR+	LR-	10%	20%	40%	Sn	Sp	LR+	LR-	10%	20%	40%
Lynch (2004)	83.0	30.0	1.19	0.57	35.3	40.6	45.9	70.4	49.9	1.41	0.59	52.0	54.0	56.1
Mahabee-Gittens (2005)	95.3	8.0	1.04	0.58	16.7	25.5	34.2	51.2	64.0	1.42	0.76	62.7	61.4	60.2
Neuman (2011)	70.0	65.4	2.02	0.46	65.9	66.3	66.8	69.6	77.1	3.03	0.39	76.4	75.6	74.9
Oostenbrink (2013)	63.4	49.8	1.26	0.73	51.2	52.5	53.9	52.8	87.5	4.23	0.54	84.0	80.6	77.1
Lipsett (2021)	81.7	52.6	1.72	0.35	55.5	58.4	61.3	60.1	79.9	2.98	0.50	77.9	75.9	74.0

LR+ = Likelihood ratio (positive test result), LR- = Likelihood ratio (negative test result), Sn = Sensitivity, Sp = Specificity.

undertaking external validation of diagnostic tools. In addition, there were several methodological refinements. The investigators used a fairly robust system of imputing missing pieces of data in their cohort, rather than using the averages of available data. Since CRP measurement was not done in all the children enrolled in the pros-pective cohort, the analysis was carried out with actual (rather than imputed) CRP values. The investigators also undertook a separate analysis of the performance of the prediction models for children younger than five years old. Limitations of the study methods and data inter-pretation are elaborated below.

The goal was to predict radiographic pneumonia among children with 'suspected community acquired pneumonia (CAP).' However, instead of employing the commonly used criteria for suspected CAP (such as the revised 2014 WHO criteria [9], or the 2012 PERCH criteria [10] among children <5y) or even the broader severe acute respiratory illness (SARI) criteria for suspected influenza [11], the investigators suspected CAP based on symptoms and signs of LRTI (which they defined as new or different cough or sputum production, chest pain, dyspnea, tachypnea, or abnormal auscultatory findings). First, it is unclear whether any one, or some, or all these criteria were required to label a child as having LRTI. Second, the relationship between these criteria (for LRTI) and the diagnosis of pneumonia is also unclear. Third, some of the components in the definition (for example sputum, chest pain, dyspnea) are oriented towards older children and adolescents; and difficult to determine in younger children and infants.

Two radiologists blinded to the clinical details, were expected to provide one among the following four reports viz., normal *X*-ray, probable or definite atelectasis, atelectasis versus pneumonia, or definite pneumonia [1]. The last two categories were used to define 'radiographic pneumonia'. Here, it is important to note that 'pneu-monia' is not a radiological finding. Therefore, it would be relevant to know what radiologic criteria were used to report an *X*-ray as having pneumonia. The paper does not clarify this point [1]. Almost two decades back, the World Health Organization (WHO) proposed radiographic pneumonia as the "presence of consolidation (further clarified as dense or fluffy opacity with or without air bronchograms), other infiltrate (evidenced by linear and patchy alveolar or interstitial densities), or pleural effusion" [12]. In fact, these criteria have been used in large studies on childhood pneumonia [13,14]. There-fore, it is intriguing why the investigators failed to define the radiologic criteria for pneumonia [1,2].

Second, the original study [2] had different reporting criteria. The fourth category therein was "probable or definite pneumonia", compared to "definite pneumonia" in the more recent publication [1]. Despite this difference, the authors reported the same number of children with radiographic pneumonia in both publications - there were 203 children with "definite pneumonia" in the recent study [1], and 203 with "probable or definite pneumonia" in the previous publication [2]. This is only possible if there were zero reports of "probable pneumonia" in the cohort of 1142 patients (which seems implausible). Third, although the recent publication [1] stated that the radiologists were blinded to the clinical details, the previous publication [2] stated that "persistent discordant interpretations" were resolved after considering the clinical interpretation, suggesting that blinding was absent at least in some cases.

Detailed examination of the five prediction tools evaluated [3-7] revealed considerable heterogeneity in the included population, enrolment criteria, basis for suspecting pneumonia clinically, definition of pneu-monia, variables studied, and the criteria used to define "radiographic pneumonia." These are summarized in **Table 2**. Given the lack of clear definitions in most of the studies [3-7], it is not

Table 2 Summary of the Characteristics of Studies From Which Prediction Models Were Derived

Study(year) reference	*Inclusion criteria*	*Criteria used to suspect pneumonia*	*Variables in the prediction model*	*Definition of radiographic pneumonia*	*No. (%) with radiographic pneumonia*
Lynch (2004) [3]	1-16y old with "clinical suspicion of pneumonia" who underwent chest x-ray (n=570). The mean/ median age was not reported.	Not defined	Fever, decreased breath sounds, crackles, tachypnea	Consensus among two of three pediatric radiologists on the presence of "pulmonary opacities". At another place, the term "focal pulmonary infiltrates" is also used.	204 (35.8)
Mahabee-Gittens (2005) [4]	2-59 mo old presenting with symptoms of LRTI who underwent chest x-ray. (*n*=510). The mean/median age was not reported, but 54.9% were <12mo.	LRTI was based on the presence of cough and >1 of: labored, rapid,or noisy breathing; chest or abdominal pain; or fever.	Age >12mo, Respiratory rate >50 /min, Oxygen saturation <96%, Nasal flaring in infants <12 mo.	Consensus among two radiologists who provided "overall clinical impressions" of pneumonia, considering the following features suggestive: "confluent opacification without volume loss, peripheral rather than central opacification, and pleural effusion". Features like hyperinflation, increased peribronchial markings, or subsegmental atelectasis, were not considered pneumonia.	44 (8.6)
Neuman (2011) [5]	<21y old with "possible pneumonia" who underwent chest x-ray in an emergency department (*n* 2574).The median (IQR) age was 2.3 (0.9–5.2) y; 73.9% were <5y.	Not described.	History of fever, history of chest pain, focal diminished breath sounds, focal rales, temperature at triage, oxygen saturation at triage, wheezing.	The final report of the attending pediatric radiologist was used to label radiographic pneumonia, which included "definite pneumonia" and also "equivocal findings of pneumonia". The former term included reports with terms such as consolidation, infiltrate, or pneumonia. The latter included terms such as "atelectasis versus infiltrate," "atelectasis versus pneumonia,"or "likely atelectasis but cannot exclude (or rule out) pneumonia." *X*-ray reports with terms like "normal chest," "normal radiograph," "clear lungs," "no acute pulmonary findings," "atelectasis," or "peribronchial cuffing," were considered as "not radiographic pneumonia".	422 (16.4)
Oostenbrink (2013) [6]	1mo-16y old presenting to the emergency department of 4 hospitals. In one hospital (Population 1), those	Not described	Ill appearance, tachypnea, oxygen saturation <94%,	*X*-rays were reported by two blinded radiologists in Population 1, a single unblinded radiologist in Population 2nd a single a blinded	Population 1:78 (15.5), Population 2:58 (13.8), Population 3:27 (7.4)

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	with fever (rectal temp >38.0) and cough were included (*n*=504); in two fever (axillary temp >38.0) and "lower respiratory signs" (cough, difficulty breathing, or wheeze were included (*n*=420); and in the fourth hospital (Population 3), those with temp >38.5) and "acute breathing were included (n=366) The respective median (IQR) ages were: 1.6 (0.8-2.9)y, 2.3 (1.2-5.5)y, and 2.3 (1.1-5.3)y.		elevated CRP.	radiologist (who could consult a colleague) in Population 3. The presence of micronodular or macronodular infiltrationsor consolidation was used to label pneumonia. If *X*-ray had not been done, "1-week noneventful follow-up" (determined either by a telephonic or personal visits, need for re-attendance, or independent review of medical records) for alternate diagnosis ruled out pneumonia.	
Lipsett (2021) [7]	3mo-18y presenting to ED with suspected pneumonia who underwent chest x-ray (n=1181). The median (IQR) age was 3.0 (1.4, 5.8)y.	Not described	Oxygen saturation at triage,presence of fever, wheeze, rales.	*X*-rays were read by a board-certified radiologist whose reports were categorized independently by three investigators as one definite of the following: pneumonia, probable pneumonia, equivocal, unlikely pneumonia, or no pneumonia. Disagreements were resolved by discussion. The first two categories were labeled as radiographic pneumonia.	206 (17.4)

CRP = serum C-reactive protein, ED = Emergency Department.

surprising that the yield of "radio-graphic pneumonia" (in a cohort of children suspected to have pneumonia), varied from, as low as 7.4% to a maxi-mum of 35.8%. This aligns with the data from a syste-matic review reporting that only 19% children with suspected pneumonia, had radiographic pneumonia in developed countries [15]. In developing countries also, the previous WHO pneumonia criteria of cough or breathing difficulty, with age specific tachypnea identified radiographic pneumonia in only a minority [16,17].

Clinical experience and the recent multi-country PERCH studies also suggest that chest radiography does not correlate with microbial etiology. In fact, in Thailand, Zambia, Bangladesh, and Mali, the most common organism identified among children with radiologically confirmed pneumonia was RSV followed by *M. tuberculosis* [18-21]. In the Gambia also, RSV dominated, although *S. pneumoniae* was a distant second [22]. In Kenya, viruses accounted for over three quarters of radiologically confirmed pneumonia, whereas bacterial etiology was seen in only 16% [23]. Even 'primary end-point pneumonia'; oft-quoted to correlate with Pneumococcal etiology, could not be accurately predicted by clinical characteristics alone [24]. A systematic review on the efficacy of Pneumococcal conjugate vaccine [25] showed that while the vaccine had 80% efficacy against vaccine-serotype invasive disease, it had only 27% efficacy against radiographic pneumonia, suggesting that the majority of radiographic pneumonia were non-bacterial.

Neither the current study [1,2] nor the previous studies [3-7] attempted to determine the microbial etiology in suspected or radiographically confirmed pneumonia. It is therefore hard to conceptualize that prediction of "radiographic pneumonia" could somehow lead to reduction in antibiotic usage, as the investigators claimed [1].

How to interpret the yield of 22.2% radiographic pneumonia among those with clinical LRTI, in this study [1]? On the one hand, this suggests that only a minority of children with (clinically suspected) pneumonia have chest *X*-ray findings, as has been shown in previous studies also. On the other hand, most children with LRTI (as per the definition used in the study) probably did not have pneumonia. In this context, the previous publication [2] provides some additional valuable insights. The median (IQR) age of children with radiographic pneu-monia was completely different from those without radiographic pneumonia (8.1 vs 2.8y), suggesting almost two different cohorts. Therefore, it is not surprising that some clinical characteristics were also quite different. For example, rhinorrhea was more frequent in those without radiographic pneumonia, whereas chest pain was more common in those with radiographic pneumonia. Interes-tingly, chest retractions were observed more often in those without radiographic pneumonia. Rhonchi and wheeze were auscultable more often in those without radiographic pneumonia, although the distinction between the two was not specified. It is also possible to argue that 22.2% may be an over-estimate as the cohort included only those children with LRTI, who underwent chest *X*-ray. In other words, there may have been children where the clinicians decided against an *X*-ray despite the clinical criteria for LRTI. The radiographic yield would be lower if such children also underwent *X*-ray.

Conclusion

There is no single mathematical model to reliably predict the presence or absence of radiographic pneumonia in children with pneumonia suspected on clinical grounds. Given the poor correlation of radiographic pneumonia with bacterial etiology (which could have reduced empiric antibiotic usage), there is no pressing reason to strive for this either.

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Pediatric Emergency Physician's Viewpoint

Ramgopal and colleagues [1] describe a sophisticated study to validate the prediction models for radiographic pneumonia in a child in the emergency department (ED). Centers for Disease Control (CDC) defines pneumonia as "an infection of the lungs that can cause mild to severe illness in people of all ages" [1]. The World Health Organization (WHO) defines pneumonia as, "In children under five years of age, who have cough and/or difficult breathing, with or without fever, pneumonia is diagnosed by the presence of either fast breathing or lower chest wall indrawing where their chest moves in or retracts during inhalation" [2]. Although, the diagnosis of pneumonia is clinical and the Infectious Disease Society of America (IDSA) does not recommend the routine use of a chest radiograph, a chest radiograph is frequently obtained in primary care and ED settings [4]. This study attempts to answer an important clinical question, can a prediction rule assist in predicting the presence of radiographic pneumonia?

An ideal clinical prediction rule requires internally and externally validated for its use across different populations after initial computation. This study is one of the first studies attempting external validation of previously published models for radiographic pneumonia. The following studies, Mahabee-Gittens, Neuman, andf Lipsett, were conducted in the United States, and thus the model attempts to validate samples from different hospitals within the same country [5-7]. At the same time, the cohort from Lynch, et al. (Canadian ED) [8] and Oostenbrink, et al. [9] (European ED) represents a sample from different countries. The inclusion, exclusion criteria, and outcome measures are well defined and can be extended to any clinical setting.

The study results are reported as the area under the receiver operating curve (AUROC) in how the various models perform [1]. The ROC curve is a plot of test sensitivity along the *y*-axis versus false positive results along the *x*-axis [10]. AUC, interpreted as the average sensitivity value for all possible specificity values, is a measure of the overall performance of a diagnostic test. Based on the results, the model of Neuman [6] exhibited the highest AUROC (0.79, 95% CI 0.75-0.82), followed by Lipsett [7] (0.76, 95% CI 0.73-0.80). In the Oostenbrink model [9], among the 432 CARPE DIEM patients with CRP data available, the AUROC of originally published coefficients was 0.55 (95% CI 0.49-0.60), which improved to 0.75 (95% CI 0.70-0.80) when using coefficients derived from the CARPE DIEM dataset.

Extension of the study results in the clinical setting is challenging for the following reasons: *a*) There is significant variability amongst the models regarding the parameters used for derivation of the pneumonia prediction rule; *b*) ROC works best when the data has a binary distribution [10]; *c*) The pneumonia prediction models fail to answer the clinical question of the probability of radiographic pneumonia in the inter-mediate-risk population; and *d*) The prediction rules have been

computed in developed countries, limiting its application in developing and resource-limited settings, where the etiology of pneumonia would also differ.

In summary, this study makes a significant effort toward validating the radiographic pneumonia prediction rule. Although the Neuman model [6] performed well, its practical application is limited due to the multiple data points that are required. The application of the Lipsett model [7] is more realistic in the clinical setting. Oostenbrink model [9] also performed well; however, the requirement of a laboratory parameter, C-reactive protein, limits its application in the clinical setting. The study reinforces that routine chest radiograph is not indicated in well-appearing patients without fever, hypoxia, and focal auscultatory findings. This can undoubtedly limit unnecessary radiation exposure and antibiotic use.

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Pediatrician's Viewpoint

Over the world, a child dies of pneumonia every 43 seconds [1]. Most of these deaths are preventable with timely diagnosis and appropriate management. Clinicians mostly rely on fever, fast breathing, lower chest indrawing and danger signs to classify and treat pneumonia with antibiotics [2]. Similar clinical picture may be seen in children with acute bronchiolitis and viral pneumonias; antibiotics are given, but do not work in these scenarios. Upper respiratory infections are mostly viral in origin, but they also often land up with prescriptions for chest *X*-rays and antibiotics. On the contrary, some cases of pneumonia may be missed due to atypical presentations. Diagnosis of pneumonia and its etiology is challenging to the clinician. The outcome considered in this study is radiological pneumonia; clinicians see pneumonias without much radiological features as well.

The clinician will surely benefit from prediction models that diagnose pneumonias accurately. Once a prediction model is developed from a data set, it is strongly recommended to evaluate the performance of the same on another data set; this process called external validation is crucial for its further use among clinicians [3]. The study has externally validated and compared five prediction models for the clinician to decide upon further use. Prediction model equations are difficult for bedside clinical use. Clinicians are more comfortable with prediction scores that include simple clinical and laboratory variables.

As the authors have rightly pointed out, these prediction models may reduce prescriptions of chest *X*-rays and antibiotics. This external validation study has opened up scope for updating these prediction models.

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