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Early View

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Title: Incorporation of biomarkers into a prediction model for paediatric radiographic pneumonia

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Abstract

Objective. To evaluate biomarkers to predict radiographic pneumonia among children with suspected lower respiratory tract infections (LRTI).

Methods. We performed a single-center prospective cohort study of children 3 months to 18 years evaluated in the emergency department with signs and symptoms of LRTI. We evaluated the incorporation of four biomarkers (white blood cell count (WBC), absolute neutrophil count (ANC), C-reactive protein (CRP), and procalcitonin), in isolation and in combination, with a previously developed clinical model (which included focal decreased breath sounds, age, and fever duration) for an outcome of radiographic pneumonia using multivariable logistic regression. We evaluated the improvement in performance of each model with the concordance (c-)index.

Results. Of 580 included children, 213 (36.7%) had radiographic pneumonia. In multivariable analysis, all biomarkers were statistically associated with radiographic pneumonia, with CRP having the greatest adjusted odds ratio of 1.79 (95% CI 1.47-2.18). As an isolated predictor, CRP at a cutoff of 3.72 mg/dL demonstrated a sensitivity of 60% and a specificity of 75%.The model incorporating CRP demonstrated improved sensitivity (70.0% vs 57.7%) and similar specificity (85.3% vs 88.3%) compared to the clinical model when using a statistically-derived cutpoint. In addition, the multivariable CRP model demonstrated the greatest improvement in c-index (0.780 to 0.812) compared with a model including only clinical variables.

Conclusion. A model consisting of 3 clinical variables and CRP demonstrated improved performance for the identification of radiographic pneumonia compared with a model with clinical variables alone.

Introduction

Lower respiratory tract infections (LRTI) are costly causes of health care visits and admissions in children [1, 2]. Community-acquired pneumonia (CAP) is one of the top 3 reasons for hospital admission from the ED in children 1-17 years old [3]. Given the substantial burden placed on children by pneumonia and the overlap in clinical features between pneumonia and other respiratory infections in children, accurate prediction of radiographic pneumonia in children carries practical value to minimize unnecessary chest radiography use. In addition, a well-performing prediction model may promote antimicrobial stewardship by limiting antibiotic use in those at low risk of radiographic pneumonia.

Models based on clinical predictors alone may facilitate the prediction of pneumonia among patients with suspected LRTI [4–7]. However, these clinical models are limited in their performance, particularly in the large proportion of patients classified as having intermediate risk of radiographic pneumonia. Several biomarkers, including c-reactive protein (CRP) and procalcitonin (PCT), have been proposed as an objective means to improve the diagnosis of pneumonia; however, biomarkers used in isolation also demonstrate limited performance [8]. The role of biomarkers may be of greatest value in children for whom the risk of pneumonia is in the moderate to severe range where decisions regarding chest radiography may be of greater importance. While professional societies do not advocate for routine chest radiography for the diagnosis and treatment of radiographic pneumonia [9, 10], the presence of radiographic pneumonia is frequently used to determine a need for antibiotics. As such, an enhanced predictive model may allow for improved antimicrobial stewardship without increasing (and possibly decreasing) the use of chest radiographs among patients at moderate risk of radiographic pneumonia. This is especially true given the recent proliferation of point-of-care biomarker assays. It is likely that that combining biomarkers with clinical prediction models for

radiographic pneumonia can improve the performance of either biomarkers or clinical features alone.

Biomarkers are not universally obtained in all patients with suspected pneumonia, due to challenges with acquisition and cost. Oostenbrink et al reported a prediction model that used C-reactive protein (CRP), in addition to physical examination findings [11]. Despite showing that CRP was important in the prediction of radiographic CAP, this study did not compare biomarkers with each other, or their use in combination. Other published prediction models that incorporated biomarkers used a composite outcome for serious bacterial infections, in which pneumonia was one of several different types of infections included. This composite outcome may limit the model's clinical utility and were underpowered to evaluate pneumonia alone [12, 13]. As objective measures, the incorporation of biomarkers may improve the diagnosis of pneumonia beyond clinical models alone, leading to reduced need for radiography and improve antimicrobial stewardship in patients at low risk.

In this study, we evaluated the role of biomarkers in improving the diagnostic accuracy of a clinical prediction model for radiographic pneumonia.

Methods

This study is a secondary analysis of a prospective cohort study (Catalysing Ambulatory Research in Pneumonia Aetiology and Diagnostic Innovations in Emergency Medicine [CARPE DIEM]) of children 3 months to 18 years of age who presented to the ED with signs and symptoms of LRTI and who had chest radiography performed for clinical suspicion of CAP. The current study builds upon our previously published prediction model for radiographic pneumonia [7]. Ethics approval for this study was obtained by the Cincinnati Children's Hospital Medical

Center Institutional Review Board (IRB #2012-4959) and the Ann and Robert H Lurie Children's Hospital of Chicago Institutional Review Board (IRB #2018-2056).

Patients with a recent hospitalization, history of aspiration, or with medical conditions that predispose to severe or recurrent pneumonia (e.g., immunodeficiency, neuromuscular disorders impacting respiration) were excluded. After obtaining informed consent from parents and assent from patients >11 years of age, demographic, historical, and physical examination data were collected from all participants. A subset of children consented for the collection of blood biomarkers, including a complete blood cell count, CRP, and PCT. Radiograph interpretations were based on consensus of two board-certified radiologists who independently reviewed all radiographs and categorized as: no atelectasis/infiltrate, definitive atelectasis, atelectasis versus pneumonia, or definitive pneumonia. Our outcome of radiographic pneumonia was defined as radiologist consensus of atelectasis versus pneumonia or definitive pneumonia [7].

We compared clinical and historical factors of included and excluded patients using Fisher's exact and Wilcoxon rank-sum tests, correcting for multiple comparisons using the Benjamini-Hochberg method. For the current study, we evaluated the incorporation of four biomarkers, individually and in combination, to our previously published clinical model [7] to predict radiographic pneumonia: white blood cell (WBC) count, absolute neutrophil count (ANC), CRP, and PCT. We included patients with at least one blood biomarker obtained. Within this subset, we performed multiple imputation with chained equations for patients with missing data [14]. We elected to perform multiple imputation instead of complete case analysis for models, as prior work has suggested that limiting models to those with complete cases can result in biased model performance [15]. However, as a sensitivity analysis, we assessed the

performance of these models on the subsets of patients with complete data for each individual biomarker. We evaluated collinearity between biomarkers in pairwise groupings. The association of each biomarker with radiographic pneumonia was evaluated using univariable logistic regression and as part of a multivariable model when incorporated into the published clinical model. Hypothesizing that there may be an additive effect of including both CRP and PCT, we evaluated a model limited to CRP and PCT, and another that included clinical variables, CRP, and PCT.

For each model, we report the concordance index (c-index), both as a raw c-index and as an optimism-corrected measure, which adjusts for potential overfitting. We report metrics of diagnostic accuracy at an optimally-derived cut point using the Euclidean distance method [16]. We constructed calibration curves to inspect the performance of the models, comparing the predicted risk to the observed pneumonia prevalence [17, 18]. As we performed multiple imputation to develop models, we assessed the performance of each when limited to complete cases for each individual biomarker (without imputation). We evaluated if any biomarkers would be retained in backwards stepwise selection bootstrapped over 1000 iterations to obtain a reduced model selected based on the lowest Akaike Information Criterion. Analyses were performed in R v4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of the 1,142 patients enrolled in the parent study, 580 patients consented to and provided blood samples; 213 (36.7%) had a diagnosis of radiographic pneumonia. Within this group, 423 (73%) patients had all four biomarkers, 32 (6%) had three biomarkers, 117 (20%) had two biomarkers, and 8 (1%) had one biomarker assessed. Compared to excluded patients, patients

who had biomarkers performed were more frequently younger, had a prolonged duration of illness and less frequently had rhinorrhoea and wheeze. Included patients had a higher proportion of radiographic pneumonia (37%) relative to excluded patients (7%; Supplementary Table 1). The median age was 4 years (interquartile range [IQR], 1.6-8.2) and 301 (52%) were boys (Table 1). The WBC, ANC, and PCT were similar between patients with and without radiographic pneumonia (Table 2). The median CRP among patients with radiographic pneumonia (4.7 mg/dL, IQR 2.1-11.4 mg/dL) was higher than in patients without radiographic pneumonia (1.7 mg/dL, IQR 0.7-3.7 mg/dL).

In univariable analyses, ANC (odds ratio [OR] 1.38, 95% CI 1.08-1.76) and CRP (OR 1.94, 95% CI 1.53-2.32) were associated with radiographic pneumonia. When adding biomarkers individually into multivariable models that included the 3 clinical variables in our original model, WBC (adjusted odds ratio [aOR] 1.58, 95% CI 1.07-2.32), ANC (aOR 1.44, 95% CI 1.06-1.96), CRP (aOR 1.79, 95% CI 1.47-2.18), and PCT (aOR 1.30, 95% CI 1.13-1.49) were all statistically associated with radiographic pneumonia (Table 3).

The clinical feature-only model demonstrated a c-index of 0.79 and an optimism-corrected c-index of 0.78 in the sample of 580 children evaluated in this study. At the optimal cut-off for predicted probability of radiographic pneumonia statistically derived from the ROC curve of 50.7%, the clinical model had a sensitivity of 57.7% and a specificity of 88.3%. When evaluating the change in model performance with the addition of biomarkers to the clinical model, the greatest improvement was found incorporating CRP, increasing the c-index to 0.83 and the optimism-correct c-index to 0.81. The CRP model had improved sensitivity (70%) and similar specificity (85%) compared with the clinical model. When assessing model performance on the subset of patients with complete data, there was a small increase in performance for each

biomarker (Supplementary Table 2). Calibration curves for the model applied to the full subset and to the cohort with complete cases are presented in Supplementary Figure 1.

Models which included these biomarkers in combination, with or without clinical variables, did not demonstrate improved performance compared to the model incorporating CRP and clinical variables. Modelling with CRP and PCT in addition to clinical variables, for example, demonstrated similar performance to the model which only contained CRP with clinical variables (raw c-index 0.83; optimism corrected, 0.81). Modelling with CRP and PCT without clinical factors demonstrated a lower c-index compared with the model incorporating CRP and clinical variables (raw c-index, 0.74; optimism-corrected, 0.72). Applying bootstrapping of all clinical and biomarker variables, three remained: age, duration of fever, and CRP (raw c-index, 0.83; optimism-corrected, 0.81).

We further evaluated the role of CRP, the strongest associated biomarker, to discriminate patients with radiographic pneumonia. When evaluating CRP as an individual predictor, the area under the ROC curve was 0.72. In ROC analysis, a CRP of 3.72 mg/dL was the optimal threshold and demonstrated a sensitivity of 60% and a specificity of 75%, though there remained substantial overlap between cases and non-cases (Supplementary Figure 2). Figure 1 illustrates the role of differing values of CRP when arbitrarily fixing the clinical predictors in a multivariable model.

Discussion

We evaluated the role of biomarkers in the prediction of radiographic pneumonia in children from a prospective cohort study, individually and in combination, with a previously derived clinical model. WBC, ANC, CRP, and PCT demonstrated a statistically significant

associations with radiographic pneumonia in multivariable models which included a single biomarker in combination with clinical variables. CRP demonstrated the strongest increase in the discriminatory performance of the clinical model from a c-index of 0.780 to 0.812. There was a modest improvement incorporating WBC, ANC, and PCT into a multivariable model. Modelling that included both CRP and PCT did not improve performance beyond a model with CRP as the sole biomarker.

The addition of CRP resulted in the strongest improvement of the clinical model, demonstrated by the largest improvements in c-index. We identified improved sensitivity (from 57.7% to 70.0%) with similar specificity (from 74.1% to 73.4%) with the model of CRP plus clinical variables compared to clinical variables alone. However, despite this improvement, the model performance a single cut-off demonstrates its limited utility when used as a one-way rule for the identification of patients at low risk of radiographic pneumonia. Instead, this model may be of greater value when clinicians are provided with continuous predictive probability of pneumonia (from 0-100%). Patients at low risk of radiographic pneumonia may not require a chest radiograph to rule out the disease, and those at very high risk may similarly not require a chest radiograph for confirmation. CRP may therefore be most advantageous for patients with an intermediate or equivocal risk when using a clinical rule in order to reduce the number of patients who fall into this category.

Our findings compare to a prior study which used both clinical data and biomarkers to identify patients with radiographic pneumonia. Oostenbrink, et al, constructed a multivariable clinical prediction model using backwards stepwise regression to predict radiographic pneumonia in 1,290 children, of whom 12.6% had radiographic pneumonia [11]. Ill appearance, tachypnoea, and an oxygen saturation <94% were retained in the final multivariable model. The

authors suggested that CRP may be of particular benefit in patients within the mid-range of model probabilities (i.e., when only a single clinical criterion is met). Our findings corroborate the improved predictive performance of a model which contains clinical data in addition to CRP.

Point-of-care CRP assays allow for in-office measurement, have comparable accuracy to laboratory assays [19] and are useful in decision-making by primary care providers in determining the need for antibiotics in adults with pneumonia [20]. Furthermore, in-office point-of-care CRP instruments may be more easily accessible to primary care clinicians and less costly compared with chest radiography, which often requires patients to travel to an additional site-of-care to have radiography performed and are more costly. Biomarker-based predictive models which demonstrate generalizability through external validation could help improve diagnostic accuracy of children deemed at moderate risk of pneumonia using clinical variables or CRP alone. Children who are at low risk for radiographic pneumonia based on the predictive model may be candidates for observation without antibiotics after shared decision-making.

PCT was associated with radiographic pneumonia in univariable and multivariable models, however the association was more modest compared to CRP. PCT has previously demonstrated modest predictive value for disease severity both among children with suspected CAP in the ED (from the CARPE DIEM cohort) [21] and in children hospitalized with CAP, with its strongest prognostic effect in differentiating those who develop the most severe outcomes from other less severe cases [22]. This association of PCT with disease severity is likely related to the ability of PCT to predict bacterial illness, whereas PCT is not as strong a predictor of radiographic pneumonia, as this may be caused by either viral or bacterial aetiologies. In one meta-analysis which evaluated the role of PCT in the diagnosis of bacterial pneumonia, PCT demonstrated an AUC of 0.70; however the outcome of bacterial pneumonia

included radiographic findings and microbiologic evidence of bacterial aetiology different from the present study focused on radiographic findings [8].

We found no additional benefit of including PCT in multivariable models for the prediction of radiographic CAP over models with clinical findings and CRP. This has been corroborated among prospective studies among adults with suspected CAP.[23] Radiographic pneumonia may be viral or bacterial in aetiology with CRP, a general marker for inflammation regardless of aetiology. PCT elevation is more correlated with bacterial aetiology. In one prospective study evaluating the role of CRP in the pre-pneumococcal vaccine era, for example, no difference was identified in CRP among patients with pneumococcal (n=57), atypical (n=43), or viral (n=29) pneumonia [24].

Our results support the premise of prior studies that WBC and ANC are of low utility in the identification of patients with radiographic pneumonia [11]. When compared with clinical models, their additive predictive power over a clinical model without biomarkers was low. Although complete blood counts are frequently obtained among children with suspected pneumonia in the ED [25], our findings are consistent with prior literature suggesting that these measures have poor discrimination between pneumonia of viral and bacterial aetiology [8] and disease severity [21, 26]. This finding also corroborates the prior model reported by Oostenbrink, et al. which noted that the addition of WBC did not improve the predictive capability of an underlying model which included clinical predictors with CRP [11].

Our findings are subject to limitations. Biomarkers were only available for a subset of patients of the overall study sample, potentially leading to ascertainment bias. Our comparison of children who did and did not receive testing for biomarkers suggested that those who had testing were of higher acuity (based on duration of symptoms, presence of oxygen desaturation, and

physical examination findings of respiratory distress). A more generalizable study would include all children suspected of pneumonia, regardless of disease acuity. However, as venepuncture is not otherwise clinically required for children with low acuity disease, there may be concerns with the feasibility of such an approach. Nevertheless, the population studied in the present investigation is also the one that will be most likely to benefit from the incorporation of biomarkers in clinical decision making. Not all biomarkers were measured among the included patients and missing data appeared to not be randomly absent with respect to our primary outcome. However, our multiple imputation models converged in our analysis, and models demonstrated similar performance when limited to patients with complete data. As with all predictive models, external validation is a requisite step prior to clinical implementation. While our outcome of interest was based on chest radiographs performed during the ED encounter, though concern might exist regarding about potentially missed cases of pneumonia during the initial presentation of illness or in children who are dehydrated [27]. Recent data in children, however, suggest that the negative predictive value for chest radiograph is high for pneumonia (98.8%), with few children with normal chest radiographs subsequently being diagnosed with pneumonia, suggesting that this phenomenon may not occur as frequently as previously thought [28]. Despite these limitations, our findings provide useful data on the additive role of biomarkers in the predictive modelling of patients with radiographic pneumonia.

In this prospective study, adding CRP to a parsimonious 3-variable clinical prediction models may have moderate utility in predicting radiographic CAP in children with LRTI. With external validation, particularly with a focus on including children that may be of lower acuity, CRP may improve discrimination of patients with pneumonia and thereby reduce utilization of chest radiography, primarily driven by improved sensitivity. These results suggest that for

patients with higher acuity disease similar to the population studied in this investigation, use of a clinical prediction model combined with CRP may be a viable solution in settings where chest radiography may be difficult to obtain, including primary care, urgent care, and potentially low resource emergency settings to guide chest imaging and antimicrobial decisions.

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Table 1. Demographics of included patient cohort. Numbers in parenthesis represent percentages (for categorical variables) or interquartile ranges (for continuous variables).

Variable	Overall (N = 580)	No Pneumonia (N = 367)	Pneumonia (N = 213)
Demographic			
Age	4 (1.6, 8.2)	2.6 (1.2, 5.6)	7.6 (3.9, 11.7)
Male sex	301 (52)	195 (53)	106 (50)
Historical			
Fever	517 (89)	314 (86)	203 (95)
Days of Fever	3 (1, 5)	2 (1, 4)	4 (2, 7)
Cough	556 (96)	348 (95)	208 (98)
Difficulty breathing	466 (80)	305 (83)	161 (76)
Fully Immunized	542 (93)	341 (93)	201 (94)
Days of illness	5 (3, 7)	4 (2, 7)	6 (3, 9)
Vomiting	310 (53)	196 (53)	114 (54)
Wheezing	343 (59)	233 (63)	110 (52)
Rapid breathing	435 (75)	288 (78)	147 (69)
Rhinorrhoea	459 (79)	310 (84)	149 (70)
Chest pain	184 (32)	98 (27)	86 (40)
Abdominal pain	200 (34)	106 (29)	94 (44)
Decreased oral intake	372 (64)	234 (64)	138 (65)
Decreased urine output	71 (12)	47 (13)	24 (11)
Smoke exposure	227 (39)	153 (42)	74 (35)
Pneumonia history	136 (23)	86 (23)	50 (23)
Past pneumonia hospitalization	57 (10)	40 (11)	17 (8)
Asthma	156 (27)	102 (28)	54 (25)
Physical examination			
Temperature (degrees Celsius)	37.6 (37, 38.4)	37.7 (37, 38.5)	37.5 (37, 38.3)
RR	36 (28, 48)	40 (30, 51.5)	32 (24, 42)
HR	142 (123, 160)	149 (131, 163)	130 (112, 148)
SBP	113 (104, 122)	114 (104, 123)	113 (104, 121)
Oxygen saturation	96 (94, 98)	96 (93, 98)	97 (94, 98)
Oxygen saturation < 92	69 (12)	46 (13)	23 (11)
Retractions	254 (45)	188 (53)	66 (32)
Grunting	54 (10)	38 (11)	16 (8)
Nasal flaring	74 (13)	50 (14)	24 (12)
Head nodding	21 (4)	18 (5)	3 (1)
Abdominal pain	68 (13)	34 (10)	34 (17)
Crackles/Rales			
None	352 (63)	228 (64)	124 (60)
Focal	159 (28)	90 (25)	69 (33)
Diffuse	51 (9)	37 (10)	14 (7)
Rhonchi			
None	369 (65)	213 (60)	156 (75)
Focal	55 (10)	33 (9)	22 (11)
Diffuse	140 (25)	111 (31)	29 (14)
Wheezing			
None	438 (78)	258 (72)	180 (87)
Focal	19 (3)	12 (3)	7 (3)
Diffuse	106 (19)	87 (24)	19 (9)

Decreased breath sounds			
None	331 (59)	233 (65)	98 (47)
Focal	172 (31)	83 (23)	89 (43)
Diffuse	60 (11)	40 (11)	20 (10)

Table 2. Summary statistics for included biomarkers.

Biomarker	No pneumonia (N = 367) Median [IQR]	Pneumonia (N = 213) Median [IQR]
WBC ($x10^9$ cells/L)	11.7 [8.4, 15.7]	11.9 [7.8, 16.8]
ANC ($x10^9$ cells/L)	6.9 [4.4, 10.9]	8.6 [5.1, 12.8]
CRP (mg/dL)	1.7 [0.7, 3.7]	4.7 [2.1, 11.4]
PCT (ng/mL)	0.25 [0.09, 0.82]	0.24 [0.09, 1.12]

White blood count (WBC) and absolute neutrophil count (ANC) data missing in 7 without pneumonia and 15 with pneumonia; C reactive protein (CRP) missing in 110 without pneumonia, 13 with pneumonia, and procalcitonin (PCT) missing in 115 without pneumonia, and 8 with pneumonia.

Table 3. Model performance on the addition of individual biomarkers to the clinical model.

	Clinical model*	**WBC**	**ANC**	**CRP**	**PCT**
Univariable OR, 95% CI	--	1.08 (0.79, 1.48)	1.38 (1.08, 1.76)	1.94 (1.63, 2.32)	1.09 (0.97, 1.21)
Multivariable OR (95% CI)*	--	1.58 (1.07, 2.32)	1.44 (1.06, 1.96)	1.79 (1.47, 2.18)	1.30 (1.13, 1.49)
C-index					
Raw	0.794	0.800	0.802	0.829	0.808
Optimism-corrected	0.780	0.783	0.786	0.812	0.795
Diagnostic performance					
Cut point of prediction model ROC curve (%)†	50.7	52.8	51.1	45.6	45.4
Sensitivity (%)	57.7	59.6	60.6	70.0	65.7
Specificity (%)	88.3	88.8	88.0	85.3	85.3
PPV (%)	74.1	75.6	74.6	73.4	72.2
NPV (%)	78.3	79.1	79.4	83.0	81.1
LR+	3.41	3.62	3.61	4.32	3.82
LR-	0.33	0.31	0.32	0.32	0.34

WBC, white blood cell; ANC, absolute neutrophil count; CRP, C-reactive protein; PCT, procalcitonin; OR, odds ratio; CI, confidence interval; c-index, calibration index; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio;
*includes variables of age, focal decreased breath sounds, and duration of fever.
†Determined by Euclidean distance method

Figure 1. Role of C-reactive protein (CRP) in risk prediction of radiographic pneumonia in a prediction model containing clinical factors (focal decreased breath sounds, duration of fever, and age) and CRP, when keeping the clinical variables fixed.

Supplementary Figure 1. Calibration plots of the each of the four studied biomarkers, both when assessed on imputed data and on the subset with complete cases. These plots assess the association between the predicted probability (X-axis) to the actual probability (Y axis) of outcome, with ideal calibration representing a line with slope 1 and X intercept at the 0. The apparent line represents in-sample calibration, and the bias-corrected line is performed via resampling to assess for out-of-sample performance.

Supplementary Figure 2. Boxplots demonstrating C-reactive protein (CRP) values among patients with and without radiographic pneumonia.

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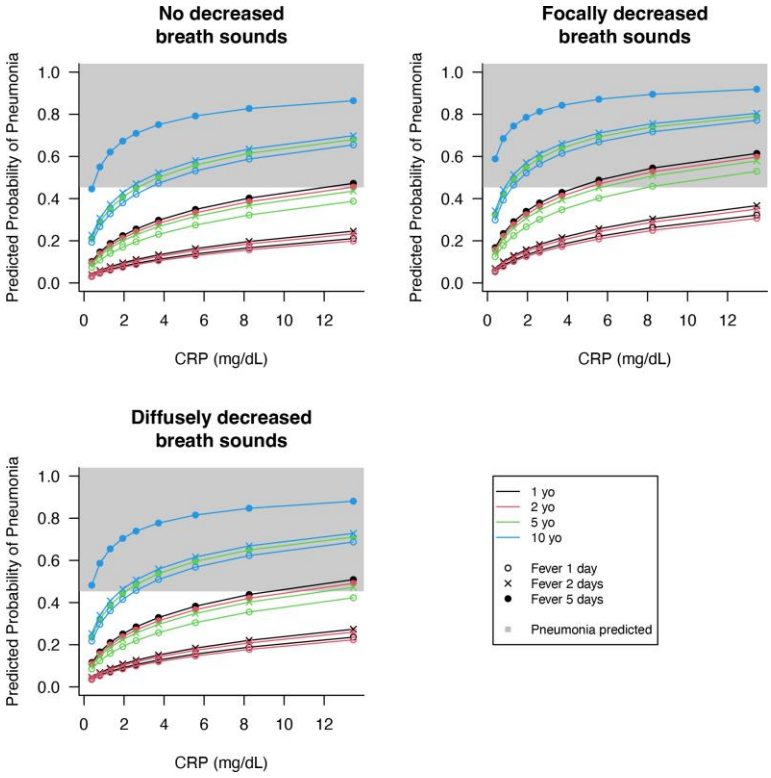
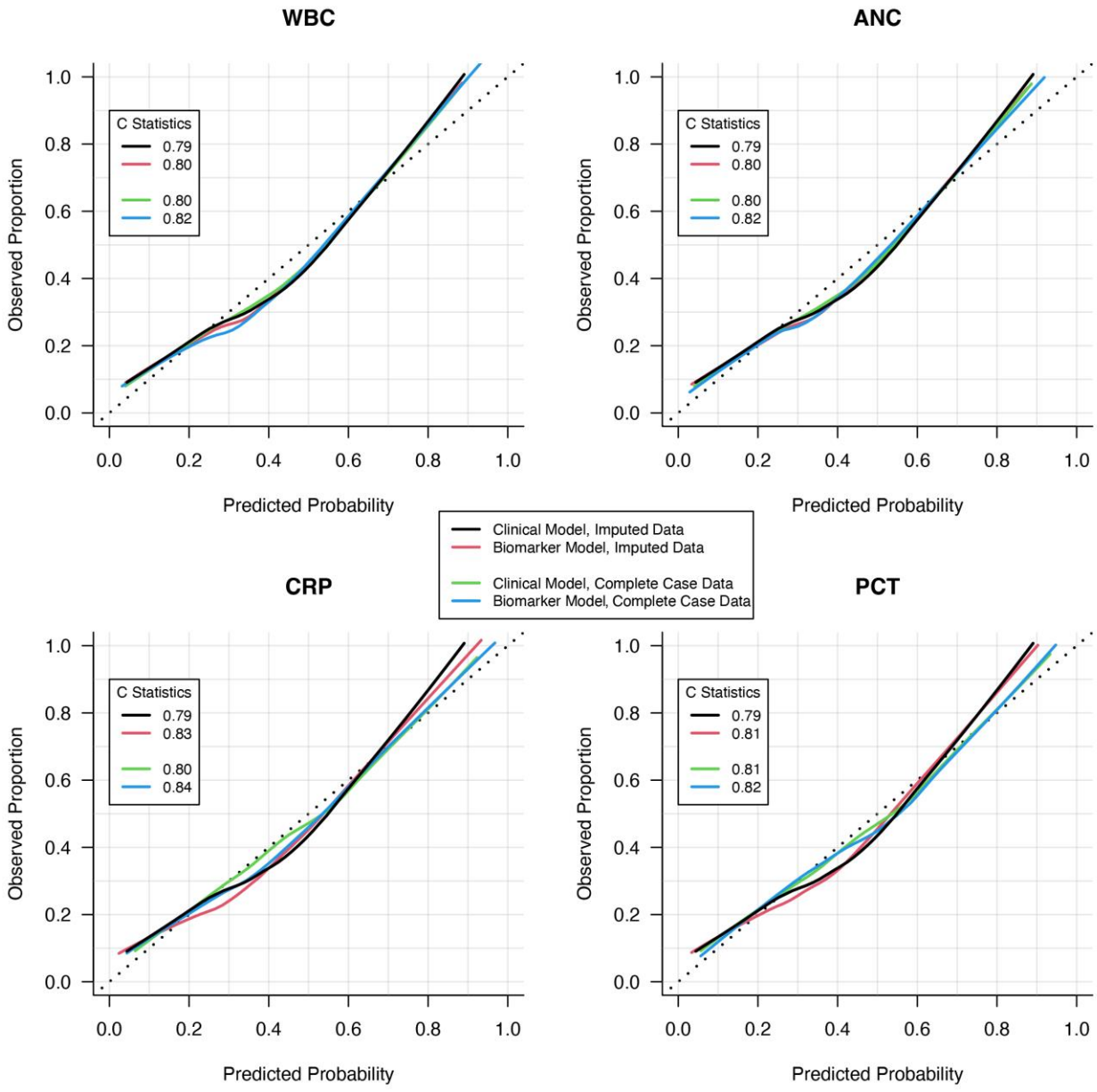
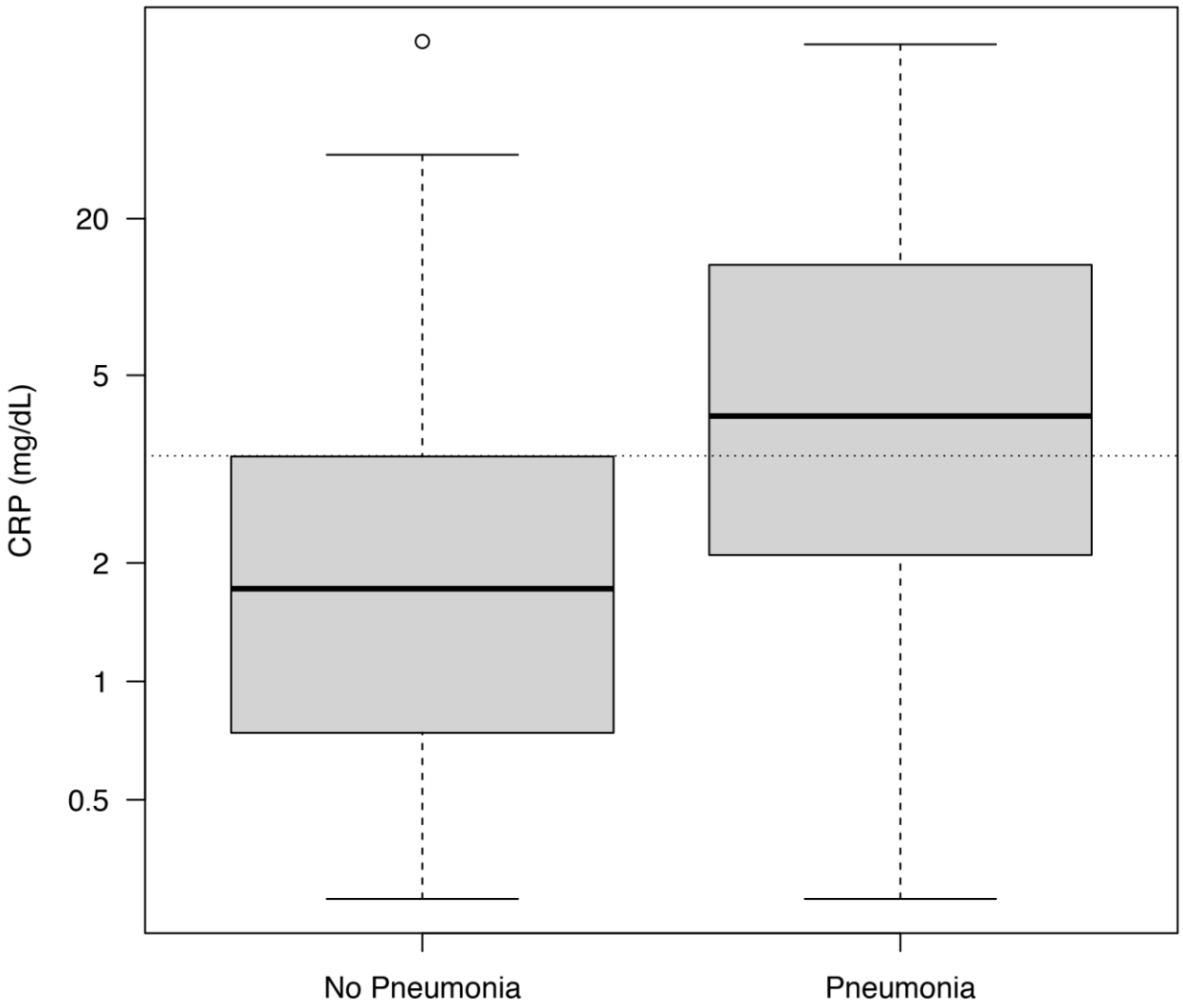

No decreased breath sounds
Focally decreased breath sounds
Diffusely decreased breath sounds
Predicted Probability of Pneumonia
CRP (mg/dL)
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
1 yo
2 yo
5 yo
10 yo
Fever 1 day
Fever 2 days
Fever 5 days
Pneumonia predicted


WBC
ANC
CRP
PCT
C Statistics
0.79
0.80
0.80
0.82
0.79
0.83
0.80
0.84
0.79
0.81
0.81
0.82
Observed Proportion
Predicted Probability
0.0
0.2
0.4
0.6
0.8
1.0
Clinical Model, Imputed Data
Biomarker Model, Imputed Data
Clinical Model, Complete Case Data
Biomarker Model, Complete Case Data


CRP (mg/dL)
20
5
2
1
0.5
No Pneumonia
Pneumonia

Supplementary Table 1. Differences between patients with and without biomarker assessment.

Variable N (%) or Median (IQR)	Overall (N = 1142)	No Biomarkers (N = 562)	At least 1 biomarker (N = 580)	P-value
Demographic				
Age	3.3 [1.4, 7.1]	2.8 [1.3, 5.7]	4 [1.6, 8.2]	<0.01
Male sex	622 (54)	321 (57)	301 (52)	0.13
Historical				
Fever	996 (87)	479 (85)	517 (89)	0.08
Days of Fever	2 [1, 4]	2 [1, 4]	3 [1, 5]	<0.01
Cough	1099 (96)	543 (97)	556 (96)	0.57
Difficulty breathing	930 (81)	464 (83)	466 (80)	0.43
Fully Immunized	1062 (93)	520 (93)	542 (93)	0.63
Days of illness	4 [2, 7]	4 [2, 7]	5 [3, 7]	<0.01
Vomiting	585 (51)	275 (49)	310 (53)	0.20
Wheezing	737 (65)	394 (70)	343 (59)	<0.01
Rapid breathing	848 (74)	413 (73)	435 (75)	0.61
Rhinorrhea	949 (83)	490 (87)	459 (79)	<0.01
Chest pain	350 (31)	166 (30)	184 (32)	0.50
Abdominal pain	362 (32)	162 (29)	200 (34)	0.07
Decreased oral intake	714 (63)	342 (61)	372 (64)	0.34
Decreased urine output	117 (10)	46 (8)	71 (12)	0.05
Smoke exposure	482 (42)	255 (45)	227 (39)	0.06
Pneumonia history	255 (22)	119 (21)	136 (23)	0.46
Past pneumonia hospitalization	101 (9)	44 (8)	57 (10)	0.32
Asthma	365 (32)	209 (37)	156 (27)	<0.01
Physical examination				
Temperature (degrees Celsius)	37.6 [37, 38.3]	37.5 [37, 38.3]	37.6 [37, 38.4]	0.20
Respiratory rate	36 [28, 48]	40 [28, 48]	36 [28, 48]	0.51
Heart rate	142 [123, 160]	142 [123, 160]	142 [123, 160]	0.94
Systolic blood pressure	114 [105, 123]	114 [106, 124]	113 [104, 122]	0.20
Oxygen saturation	96 [94, 98]	97 [95, 98.2]	96 [94, 98]	0.02
Oxygen saturation < 92	93 (8)	24 (4)	69 (12)	<0.01
Retractions	488 (44)	234 (43)	254 (45)	0.51
Grunting	78 (7)	24 (4)	54 (10)	<0.01
Nasal flaring	127 (12)	53 (10)	74 (13)	0.12
Head nodding	34 (3)	13 (2)	21 (4)	0.30
Abdominal pain	104 (10)	36 (7)	68 (13)	<0.01
Crackles/Rales				<0.01
None	761 (69)	409 (75)	352 (63)	
Focal	240 (22)	81 (15)	159 (28)	
Diffuse	107 (10)	56 (10)	51 (9)	
Rhonchi				<0.01
None	715 (64)	346 (63)	369 (65)	
Focal	83 (7)	28 (5)	55 (10)	
Diffuse	311 (28)	171 (31)	140 (25)	
Wheezing				<0.01
None	776 (70)	338 (62)	438 (78)	
Focal	38 (3)	19 (3)	19 (3)	
Diffuse	296 (27)	190 (35)	106 (19)	
Decreased breath sounds				<0.01
None	729 (66)	398 (73)	331 (59)	

Focal	257 (23)	85 (16)	172 (31)	
Diffuse	123 (11)	63 (12)	60 (11)	
Radiographic pneumonia	253 (22)	40 (7)	213 (37)	<0.01

P-values are corrected at false discovery rate of 0.05 via the Benjamini-Hochberg method.

Supplementary Table 2. Model performance on the addition of individual biomarkers to the clinical model on subsets of data with complete data only

Characteristic	WBC	ANC	CRP	PCT
N with complete data	541	541	445	444
Prevalence of pneumonia (%)	200 (37)	200 (37)	194 (44)	199 (45)
C-index				
Raw	0.819	0.816	0.837	0.824
Optimism-corrected	0.797	0.794	0.815	0.800
Diagnostic performance				
Sensitivity	0.665	0.660	0.686	0.673
Specificity	0.868	0.856	0.876	0.824
Positive predictive value	0.747	0.729	0.811	0.757
Negative predictive value	0.815	0.811	0.783	0.757
Positive likelihood ratio	5.04	4.59	5.55	3.84
Negative likelihood ratio	0.39	0.40	0.36	0.40

WBC, white blood cell; ANC, absolute neutrophil count; CRP, C-reactive protein; PCT, procalcitonin