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Utility of inflammatory markers in predicting the aetiology of pneumonia in children

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ABSTRACT

We aimed to investigate the diagnostic value of applying cut-off levels of inflammatory markers and to develop a prediction model for differentiation between bacterial and viral infections in paediatric community-acquired pneumonia based on C-reactive protein (CRP), neutrophil, and white cell counts (WCC). Amongst 401 children, those with bacterial pneumonia were older than those with viral pneumonia ($P < 0.001$). Compared to viral, bacterial infections had a higher median CRP level ($P < 0.001$), whereas WCC and neutrophil count were not different. Bacterial infections were associated with higher CRP >80 mg/L than viral infections ($P = 0.001$), but levels <20 mg/L were not discriminatory ($P = 0.254$). Receiver operating characteristic curve of the model for differentiating bacterial from viral pneumonia based on age, CRP, and neutrophil count produced area under the curve of 0.894 with 75.7% sensitivity and 89.4% specificity. This aetiological discriminant prediction model is a potentially useful tool in clinical management and epidemiological studies of paediatric pneumonia.

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1. Introduction

Use of C-reactive protein (CRP) and white cell count (WCC) either individually or collectively has not been shown to accurately differentiate between bacterial and viral aetiology of pneumonia in children (Don et al., 2009). However, meta-analysis data have suggested that despite its low sensitivity, CRP could be useful for both ruling in and ruling out serious bacterial infections, including pneumonia, in children presenting with fever (Flood et al., 2008; Sanders et al., 2008). A CRP level of >80 mg/L has a significant positive likelihood ratio on ruling in systemic bacterial infections, whereas values <20 mg/L likely rule out these infections (Van den Bruel et al., 2011). In contrast, WCC was not identified as a significant marker in including or excluding serious infections (Van den Bruel et al., 2011).

Availability of CRP as a point-of-care test giving an immediate result helped clinicians in primary care settings to prescribe fewer antibiotics for lower respiratory tract infections (Cals et al., 2009). Prediction of the causative pathogens of pneumonia could assist targeted management and facilitate appropriate antibiotic selection (Craig et al., 2010; Ruiz-Gonzalez et al., 2000). We therefore analysed data from 2 aetiological studies of community-acquired pneumonia in children (Elemraid et al., 2013), aiming to develop a prediction model to differentiate between bacterial and viral aetiology based on CRP, total WCC, and absolute neutrophil count. We also investigated the diagnostic value of applying defined cut-off levels of these inflammatory markers for differentiation between bacterial and viral infections.

2. Materials and methods

2.1. Participants

Two prospective aetiological studies of hospitalised children aged ≤16 years with community-acquired pneumonia during August 2001 to July 2002 and October 2009 to March 2011 were undertaken at the Newcastle Hospitals and South Tees Hospitals NHS Foundation Trusts (Elemraid et al., 2013). Recruitment methodology and enrolment criteria were consistent across the 2 studies and included children with signs and symptoms suggestive of lower respiratory tract infection and chest radiographic findings consistent with pneumonia as determined by the admitting paediatrician.

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Exclusions were hospitalisation in the preceding 3 weeks in order to rule out hospital-acquired pneumonia, clinical bronchiolitis, or normal chest radiograph after formal reporting by a radiologist. Informed written consent was obtained from parents. Ethical and Caldicott approvals were granted (Newcastle and North Tyneside Research Ethics Committee [No: 08/H0906/105], and Research Approval Board at South Tees Hospitals NHS Foundation Trust [No: 2008075]).

2.2. Radiology and laboratory procedures

Chest radiographs were reported by radiologists and classified according to the WHO criteria of lobar, patchy, or perihilar infiltrates (Cherian et al., 2005). All films were reviewed by second consultant radiologists (1 for each study) at the regional centre in Newcastle. Microbiological and virological testing informed the aetiology of pneumonia (Elemraid et al., 2013). Identified pathogens were categorised as viral, bacterial, or mixed viral-bacterial infections according to defined diagnostic criteria (online supplement). Inflammatory markers included CRP, total WCC, and absolute neutrophil count.

2.3. Statistical analysis and model development

Univariate analyses of age of children and inflammatory markers including CRP, WCC, and neutrophil count for bacterial (typical and atypical) and viral infections were summarised using median with interquartile range (IQR) and Kruskal-Wallis test to test significance. Mixed bacterial-viral infections were excluded from the analysis to avoid potential bias to the findings. Data were analysed individually for each study and jointly to increase the power. Similar subgroup analysis using the same variables was conducted to investigate if they can differentiate typical from atypical pneumonia after exclusion of mixed bacterial-viral and typical-atypical bacterial infections to make the comparison as accurate as possible.

Cut-off levels of CRP >80 mg/L and <20 mg/L were used to respectively rule in and rule out a bacterial cause of pneumonia, whereas levels of WCC $>15 \times 10^9$/L and neutrophil count $>10 \times 10^9$/L were applied to investigate their association with or ability to rule in bacterial infections (Van den Bruel et al., 2011). Fisher's exact test with odds ratios (ORs) and 95% confidence intervals (CIs) was used to measure the association between the categorical variables for bacterial and viral infections. Multivariate logistic regression analysis (outcome: bacterial pneumonia) included those variables, which were significant ($P < 0.05$) in the preceding univariate analyses.

Discriminant analysis was used to classify cases on the basis of age, CRP, WCC, and neutrophil count forming the basis of selecting the best combination for predicting bacterial infections in children with community-acquired pneumonia. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for all predictors as continuous variables for the distinction between bacterial and viral pneumonia (Griner et al., 1981). The diagnostic performance of the model for bacterial infection was evaluated by constructing a receiver operating characteristic (ROC) curve based on estimated probability of bacterial aetiology in relation to the biomarkers (Zweig and Campbell, 1993). The C-statistic, which is area under the curve (AUC), was used as an overall indicator of test performance to select the best model to predict bacterial pneumonia amongst the predictors either singly or combined (Hanley and McNeil, 1982). Bacterial infections were analysed against viral infections in order to test the model accuracy for not missing serious infection.

Descriptive data analysis was completed using Epi Info™ 7 (Centers for Disease Control and Prevention, Atlanta, GA, USA). The R statistical software version 2.15.1 (The R Foundation for Statistical Computing, Vienna, Austria) was used for analysis of model development.

3. Results

A total of 241 and 160 children were enrolled in 2002 and 2011 studies, respectively, of whom 57% were males and 73% aged <5 years. The aetiological characteristics of pneumonia and pneumococcal serotype distribution of this cohort have been presented previously (Elemraid et al., 2013). Lobar consolidation was more often reported in 2011 study (61%) compared to 23% in 2002 study ($P < 0.001$). Likely infections were established in 53% children; 24% were viral, 21% bacterial, and 8% mixed viral-bacterial. Respective identified infections between 2002 and 2011 studies were bacterial (24% and 17.5%) ($P = 0.258$), viral (19.5% and 31%) ($P = 0.021$), and mixed (5% and 12.5%) ($P = 0.015$).

There was no overall difference in the number of pneumococcal infections identified between both studies ($P = 0.557$). They represent 17.4% amongst children tested in 2011 study (14/93 [15%] and 10/45 [22.2%] in those aged under and over 5 years, respectively). This was compared to 14.7% in 2002 study (28/180 [15.6%] and 7/58 [12%] amongst those under and over 5 years old, respectively). A serotype was identified in 75% (18/24) in 2011 study. These were serotypes 1 (44.4%), 3 (27.8%), 19A (22.2%), and 7A/F (5.6%) (Elemraid et al., 2013).

Group A streptococcal infections were confirmed in higher proportion of children (10.5%) in 2011 study than 2002 study (7%). *Mycoplasma pneumoniae* was identified from acute serology in 9.9% of children in 2011 study, with 4% (2/51) in those aged under 5 years and 20% (6/30) over 5 years old. The rate of detected mycoplasma infection was higher in 2002 study (12.5%) when paired acute and

Table 1
Median values of age and inflammatory markers for bacterial (typical and atypical) and viral infections.

	Infection category, median (IQR) [n]			Multivariate analysis[a]	
Variable	Bacterial	Viral	*P*-value	OR (95% CI)	*P*-value
2001–2002 study					
Age (years)	44.5 (1.0–6.0) [57]	2.0 (1.5–3.0) [47]	0.005	1.2 (1.04–1.49)	0.016
CRP (mg/L)	90.5 (17.5–249.5) [40]	26.5 (7.0–67.0) [35]	0.004	1.0 (0.99–1.01)	0.309
White cell count ($\times 10^9$/L)	17.0 (12.5–23.0) [47]	12.5 (8.0–17.0) [42]	0.012	1.1 (0.95–1.20)	0.271
Neutrophil count ($\times 10^9$/L)	13.5 (8.0–16.5) [46]	7.0 (3.5–10.5) [40]	0.005	1.0 (0.87–1.19)	0.806
2009–2011 study					
Age (years)	5.7 (2.6–11.3) [28]	1.4 (0.8–2.3) [49]	<0.001	1.3 (1.01–1.59)	0.042
CRP (mg/L)	239.5 (96.0–296.0) [27]	54.0 (25.0–83.0) [37]	0.0001	1.01 (1.002–1.017)	0.009
White cell count ($\times 10^9$/L)	17.8 (12.2–22.8) [27]	13.1 (9.6–18.6) [39]	0.042	0.8 (0.59–1.15)	0.267
Neutrophil count ($\times 10^9$/L)	13.5 (9.4–19.1) [27]	7.9 (4.7– 13.3) [39]	0.003	1.3 (0.88–1.91)	0.190
Both studies combined					
Age (years)	5.0 (2.2–8.1) [85]	1.4 (1.0–2.5) [96]	<0.001	1.3 (1.12–1.49)	0.0004
CRP (mg/L)	165.5 (24.0–267.0) [67]	40.0 (15.0–81.5) [72]	<0.001	1.007 (1.002–1.011)	0.006
White cell count ($\times 10^9$/L)	17.4 (12.1–22.9) [74]	12.6 (9.1–17.0) [81]	0.002	1.04 (0.94–1.15)	0.467
Neutrophil count ($\times 10^9$/L)	13.0 (7.7–16.5) [73]	7.3 (4.5–11.7) [79]	0.0001	1.01 (0.89–1.16)	0.849

[a] Multivariate analysis (outcome: bacterial pneumonia) included age, CRP, WCC, and neutrophil count.

Table 2
Comparison of cut-off levels of inflammatory markers between bacterial (typical and atypical) and viral infections.

Inflammatory markers	Bacterial infection, n (%)	Viral infection, n (%)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
2001–2002 study						
CRP (>80 mg/L)	22 (55)	7 (20)	0.2 (0.07–0.58)	0.002	2.1 (0.61–7.19)	0.243
CRP (<20 mg/L)	11 (27.5)	15 (42.9)	1.9 (0.75–5.19)	0.225	–	–
WCC (>15 × 10^9/L)	27 (57.5)	15 (35.7)	0.4 (0.17–0.97)	0.056	–	–
Neutrophils (>10 × 10^9/L)	26 (56.5)	8 (20)	0.2 (0.07–0.51)	0.0008	10.7 (2.56–44.81)	0.001
2009–2011 study						
CRP (>80 mg/L)	21 (77.8)	11 (29.7)	0.1 (0.04–0.38)	0.0003	6.8 (2.08–22.05)	0.001
CRP (<20 mg/L)	4 (14.8)	8 (21.6)	1.6 (0.42–5.93)	0.537	–	–
WCC (>15 × 10^9/L)	16 (59.3)	15 (38.5)	0.4 (0.16–1.17)	0.133	–	–
Neutrophils (>10 × 10^9/L)	17 (63)	14 (36)	0.3 (0.12–0.91)	0.045	1.9 (0.62–6.31)	0.246
Both studies combined						
CRP (>80 mg/L)	43 (64.2)	18 (25)	0.2 (0.09–0.39)	0.000004	3.6 (1.65–8.07)	0.001
CRP (<20 mg/L)	15 (22.4)	23 (32)	1.6 (0.76–3.47)	0.254	–	–
WCC (>15 × 10^9/L)	43 (58)	30 (37)	0.4 (0.22–0.81)	0.010	0.5 (0.13–1.96)	0.320
Neutrophils (>10 × 10^9/L)	43 (59)	22 (27.8)	0.3 (0.14–0.53)	0.0001	5.9 (1.47–23.94)	0.012

convalescent samples were available, with 7% (9/128) in those under 5 and 27% (13/48) over 5 years old (Elemraid et al., 2013).

Table 1 shows the median values of inflammatory markers by infection type. Children with bacterial pneumonia (typical and atypical) were older than those with viral pneumonia ($P < 0.001$). Compared to viral infections, bacterial infections had higher median level [IQR] of CRP (165.5 [24.0–267.0] versus 40.0 [15.0–81.5], $P < 0.001$), WCC (17.4 [12.1–22.9] versus 12.6 [9.1–17.0], $P = 0.002$), and neutrophil count (13.0 [7.7–16.5] versus 7.3 [4.5–11.7], $P = 0.0001$). On multivariate analysis, only age and CRP level remained significantly different between both groups. Overall, bacterial infections had a CRP >80 mg/L more often than viral infections (OR 3.6, 95% CI 1.65–8.07, $P = 0.001$), but levels <20 mg/L were not different between bacterial and viral infections ($P = 0.254$). Neutrophil count >10 × 10^9/L was associated with bacterial more than viral pneumonia ($P = 0.012$), whereas WCC >15 × 10^9/L did not differ between bacterial and viral pneumonia ($P = 0.320$) (Table 2).

In the subgroup analysis of children with typical pneumonia (n = 60) and atypical pneumonia (n = 19), only CRP level remained significantly different between both groups on multivariate analysis. Compared with atypical pneumonia, typical pneumonia was more often associated with high median level of CRP (235.0 [81.0–294.0] versus 20.0 [11.0–36.0], $P = 0.006$) and levels >80 mg/L (OR 9.5, 95% CI 1.57–58.16, $P = 0.014$). In view of sample size of this subgroup as reflected in wide confidence interval, prediction analysis using ROC curve was not performed to avoid biased findings.

Table 3 shows the sensitivity, specificity, and predictive values for all predictors that were tested for inclusion in the model for the distinction between bacterial and viral infections. Neutrophil count as a single predictor produced the best AUC of 0.859 followed by WCC 0.806, CRP 0.799, and age 0.775. The ROC validation curve of the model for differentiating bacterial from viral pneumonia based on age, CRP, and neutrophil count produced AUC of 0.894 with 75.7% sensitivity and 89.4% specificity. This model has 91.4% PPV and 71.2% NPV (Fig.). Addition of WCC in this model or replacing neutrophil count with WCC produced prediction models with similar sensitivity (74.3%), specificity (89.4%), PPV (91.2%), NPV (70.0%), and AUC (0.898). As the models produced similar AUC, we selected the aforementioned model because it includes neutrophil count, which when tested alone, it produced better AUC than WCC.

Table 3
Overall diagnostic value of age and inflammatory markers as continuous variables in predicting typical and atypical bacterial pneumonia.

Variable	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
Age (years)	72.9	70.2	78.5	63.5	0.775
CRP (mg/L)	90.0	68.1	80.8	82.1	0.799
WCC (×10^9/L)	62.9	87.2	88.0	61.2	0.806
Neutrophil count (×10^9/L)	77.1	88.1	88.5	71.4	0.859

4. Discussion

The present study describes a laboratory-based prediction model using a minimal number of variables to identify bacterial pneumonia. Our data indicate that children with bacterial pneumonia had higher levels of CRP and were older than those with viral pneumonia. A discriminant prediction model including age, CRP, and WCC/neutrophil count is a potentially useful tool in assisting clinicians to make decisions about antibiotic treatment and duration for suspected community-acquired pneumonia in children. This is supported with good positive (91.4%) and negative (71.2%) predictive values of the model on detecting those with and without bacterial infections.

Similar to recent pooled review data (Van den Bruel et al., 2011), applying diagnostic cut-off levels for CRP, WCC, and neutrophil count

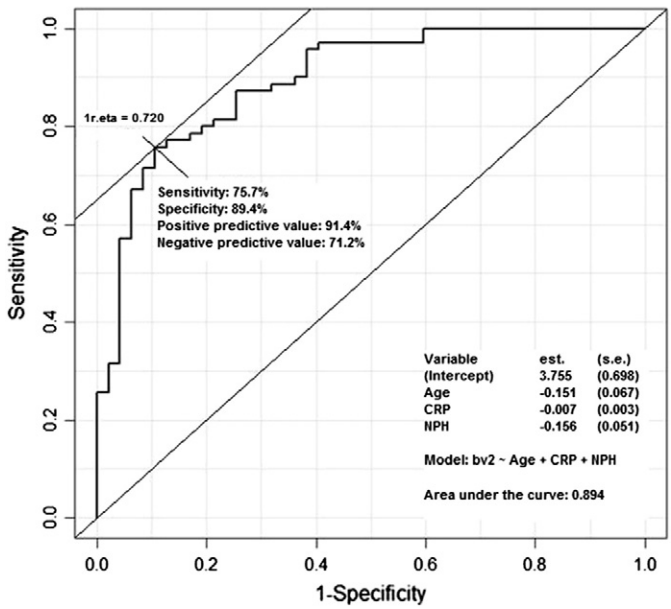

Fig. ROC curve for aetiological prediction model of bacterial pneumonia including age, CRP, and neutrophil count (NPH).

showed that the CRP performed better at ruling in than ruling out bacterial infections in hospitalised children with pneumonia. It was concluded that CRP >80 mg/L is likely to rule in bacterial infection, whereas CRP <20 mg/L is required to exclude serious bacterial infection (Van den Bruel et al., 2011). There is, however, still a 15% risk of having a CRP <80 mg/L and a serious infection (Andreola et al., 2007). Bleeker et al. (2007) proposed a prediction rule including CRP, WCC, and urinalysis data that improved the prediction probability of serious bacterial infection in children with fever without focus from 4% to 54%. Other studies have used higher CRP levels >40–150 mg/L to predict serious bacterial infections in children (Flood et al., 2008; Virkki et al., 2002) and to differentiate between typical and atypical pneumonia (Prat et al., 2003). It has been asserted that single CRP measurements lack accuracy to predict serious bacterial infections in young children with serial readings being helpful to monitor trends (McWilliam and Riordan, 2010). We found that lower values of neutrophil count can be observed in both bacterial and viral pneumonia, whereas higher levels (>10 × 10^9/L) are highly specific for bacterial infections (Van den Bruel et al., 2011).

Clinical assessment is vital and clinical features are reported as discriminators for serious bacterial infection. In a large prospective study, a computerised diagnostic model of clinical features improved accuracy in identifying potential serious bacterial infections (Craig et al., 2010). In a previous study in our setting (Nademi et al., 2001), bacterial infections were identified in 29% of children, and only history of poor feeding or restlessness was significant predictor. Therefore, combining a prediction model and defined cut-offs with clinical findings could enhance the diagnosis of likely causative pathogens of pneumonia in children (Nijman et al., 2013; Oostenbrink et al., 2013).

Discriminant analysis relies on assumption of normality distribution (Spruijt et al., 2013; Zweig and Campbell, 1993). Using prediction rules with different both cut-offs and age groups is impractical particularly at centres with high turnover of patients. Age is continuously distributed and if were categorised this would provide arbitrary level and offend the assumption of normality. Also, when developing prediction models of bacterial infections in children with fever, it is suggested that continuous variables should stay as such (Spruijt et al., 2013). A solution could be computer-assisted software (app) into which the raw continuous data were entered to make it more acceptable for use by clinicians. If such a tool was developed, validation in different primary and secondary settings using different populations would be required before it would be suitable for clinical application (Oostenbrink et al., 2012).

4.1. Strengths and limitations

The strength of this study is that robust laboratory investigations were used to identify the aetiology of radiologically confirmed pneumonia in children and thus distinguish bacterial from viral infections (Elemraid et al., 2013). Data were collected prospectively from 2 consecutive studies within the same populations using the same standardised methodology, enrolment definitions, and defined diagnostic criteria. Our proposed model includes the minimum number of predictor variables, which makes it clinician-friendly for use in busy day-to-day practise.

Limitations include lack of inclusion of children in primary care settings. As all children with suspected pneumonia received antibiotic treatment at their admission to hospital, it could be argued that bacterial infection was felt to be likely in the view of admitting staff. Use of cut-off levels for inflammatory markers can create diagnostic uncertainty when values fall between upper and lower cut-off levels. Although procalcitonin previously showed better diagnostic accuracy over CRP for bacterial infections (Moulin et al., 2001; Simon et al., 2004, 2008), our goal was to investigate if we could use routinely measured markers to predict the aetiology of pneumonia. At the time of this study, procalcitonin was not routinely available or used at the involved sites. Prediction models cannot deliver perfect diagnostic accuracy, and clinical and laboratory prediction rules should not replace clinical assessment. The overlap between bacterial and viral infections adds further limitation to the application of diagnostic cut-off levels and prediction rules. This effect on the data is likely to be minimised by the exclusion of mixed viral-bacterial infections from the analyses. Finally, the sample size for atypical bacterial infections is relatively small, although the study had enough power to detect differences between groups of infections.

In conclusion, an aetiological discriminant prediction model including age, CRP, and WCC/neutrophil count is a potentially useful tool in clinical management and epidemiological studies of paediatric pneumonia. Using CRP alone can aid in ruling in or ruling out bacterial infections when defined cut-off levels are applied. Future prospective studies including primary and secondary care settings are required to investigate the application of these 2 approaches in conjunction with other clinical features.

Contributors

JEC developed the study concept. MAE and JEC collected and managed the data. MAE performed statistical analysis under guidance and supervision of epidemiologist SPR. All authors were involved in the interpretation of the results and writing of this manuscript.

Conflicts of interest and source of funding

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