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External validation of a multivariable prediction model for identification of pneumonia and other serious bacterial infections in febrile immunocompromised children

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Abstract

Objective

To externally validate and update the *Feverkids* tool clinical prediction model for differentiating bacterial pneumonia and other serious bacterial infections (SBIs) from non-SBI causes of fever in immunocompromised children.

Design

International, multicentre, prospective observational study embedded in PErsonalised Risk assessment in Febrile illness to Optimise Real-life Management across the European Union (PERFORM).

Setting

Fifteen teaching hospitals in nine European countries.

Participants

Febrile immunocompromised children aged 0-18 years.

Methods

The *Feverkids* clinical prediction model predicted the probability of bacterial pneumonia, other SBI or no SBI. Model discrimination, calibration and diagnostic performance at different risk thresholds were assessed. The model was then re-fitted and updated.

Results

Of 558 episodes, 21 had bacterial pneumonia, 104 other SBI, and 433 no SBI. Discrimination was 0.83 (95%CI 0.71-0.90) for bacterial pneumonia, with moderate calibration and 0.67 (0.61-0.72) for other SBIs, with poor calibration. After model re-fitting, discrimination improved to 0.88 (0.79-0.96) and 0.71 (0.65-0.76) and calibration improved. Predicted risk <1% ruled out bacterial pneumonia with sensitivity 0.95 (0.86-1.00) and negative likelihood ratio (LR) 0.09 (0.00-0.32). Predicted risk >10% ruled in bacterial pneumonia with specificity 0.91 (0.88-0.94) and positive LR 6.51 (3.71-10.3). Predicted risk <10% ruled out other SBIs with sensitivity 0.92 (0.87-0.97) and negative LR 0.32 (0.13-0.57). Predicted risk >30% ruled in other SBIs with specificity 0.89 (0.86-0.92) and positive LR 2.86 (1.91-4.25).

Conclusion

Discrimination and calibration were good for bacterial pneumonia but poorer for other SBIs. The rule-out thresholds have the potential to reduce unnecessary investigations and antibiotics in this high-risk group.

Introduction

Children with immunocompromising conditions, including primary immunodeficiencies (PID) or immunodeficiencies secondary to malignancy, transplantation, chemotherapy and immunosuppressive drugs, are at high risk (HR) of serious bacterial infections (SBI) [1-3]. They may present with atypical features [4] and fever may be the only sign of infection [5]. They may also develop fever due to viral, fungal and non-infectious causes [6].

Differentiating between causes of fever in immunocompromised children is a challenge which results in frequent usage of empirical broad-spectrum antibiotics, which has reduced mortality but contributes to antimicrobial drug resistance [7]. There is a need for clinical prediction tools for SBI in this high-risk population.

Clinical prediction models have been developed for the emergency department setting to assist in identifying the small number of children with SBIs [8-10]. However, these studies largely excluded children with immunocompromise, as do UK guidelines [11]. While prediction models have been derived [12-18] and validated [19] for children with febrile neutropenia, these are not in routine clinical use and they do not address fever in non-neutropenic immunocompromised patients.

The *Feverkids* tool clinical prediction model uses clinical variables available at presentation and admission C-reactive protein (CRP) to predict the risk of bacterial pneumonia and other serious bacterial infections (SBI). The model was derived in two populations of febrile children presenting to ED in the Netherlands and externally validated in the UK [8]. It has since been further externally validated [20] and assessed for impact [21, 22]. Patients with immunocompromise were excluded during development, although a recent predictive model for invasive bacterial infection (IBI) based on *Feverkids* variables included children with comorbidities including immunocompromise [23].

This study externally validates the *Feverkids* tool clinical prediction model in immunocompromised children.

Methods

This prospective, international, multicentre, observational study is embedded within the Personalised Risk assessment in Febrile illness to Optimise Real-life Management across the European Union (PERFORM) study [24]. Reporting is in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines (Appendix 1).

Participants

Recruitment was between 2nd June 2016 and 31st December 2019. Children <18 years old were eligible for inclusion if they had an immunocompromising condition and presented to a participating hospital's emergency department, ward or intensive care unit with fever ≥38.0°C, history of fever within 72 hours, or suspicion of infection, and had a clinical indication for blood investigations. Participants could have multiple episodes a minimum of two weeks apart.

Immunocompromising conditions included primary immunodeficiency or secondary immunodeficiency, haematological or solid organ malignancy, human immunodeficiency virus (HIV), haematopoietic or solid organ transplant, or receipt of immunosuppressive medications or chemotherapy within the last two weeks.

Participants were recruited from fifteen tertiary centres in nine countries: four sites in the United Kingdom and the Netherlands and one site in Austria, Germany, Greece, Latvia, Slovenia, Spain, and Switzerland. Eight patients recruited to a site in The Gambia were excluded. Participant involvement lasted for the illness episode plus 28 days.

Outcome measures

Diagnosis was made by experienced paediatricians following a reference standard [25]. This classifies episodes into one of eleven phenotypes: definite bacterial, probable bacterial, bacterial syndrome, unknown bacterial/viral, viral syndrome, probable viral, definite viral, trivial illness, other infection, uncertain infection/inflammation, or inflammatory syndrome. All centres had training in applying the reference standard and difficult classifications were discussed with consortium experts.

To compare with the original model study [8], these phenotypes were further grouped into three categories: bacterial pneumonia, other serious bacterial infections (other SBIs) and no SBI.

Bacterial pneumonia was diagnosed in PERFORM 'definite/probable bacterial/bacterial syndrome' cases where there were clinical symptoms compatible with acute respiratory infection and radiological evidence of bacterial pneumonia.

Other SBIs were diagnosed in PERFORM 'definite/probable bacterial/bacterial syndrome' cases where there was a positive blood, urine or cerebrospinal fluid culture, or localising features of infection indicative of a serious bacterial infection (e.g. cellulitis, meningitis, abscess, urinary tract infection, bacterial upper respiratory tract infection, osteomyelitis or infectious diarrhoea with a pathogenic stool organism). Uncomplicated pharyngitis, cystitis and soft tissue infection without systemic features were not included as other SBIs.

'No SBI' was diagnosed in the absence of bacterial pneumonia or other SBI. This included probable or definite viral illness, a non-infectious cause, or an uncertain diagnosis. Episodes of febrile neutropenia without a positive sterile-site culture, sepsis syndrome or localising symptoms of bacterial infection were classified as having no SBI. Patients with parasitic infection were excluded.

The detailed clinical phenotypes of the PERFORM HR cohort are described in van der Velden et al. [26].

Predictor variables

The *Feverkids* clinical prediction model uses eleven predictor variables which are available at the time of presentation: age, sex, temperature, duration of fever, tachycardia, tachypnoea, ill appearance, chest wall retractions, prolonged capillary refill time (>3 seconds), oxygen saturation <94%, and C-reactive protein [8] (Appendix 2). The prediction model was applied to calculate the predicted risk of bacterial pneumonia and of other SBIs as a group.

Statistical analysis

Statistical analysis was performed in R 4.0.5. The required sample size to validate the model was calculated [27]. Missing values were imputed 10 times using Multiple Imputation by Chained Equations

[28]. The imputation model included all predictor variables, diagnostic outcome, recruitment site, category of immunosuppressive condition and whether the patient was receiving immunosuppressive drugs/chemotherapy, had neutropenia with neutrophils <0.5 x 10^9/L or had any NICE red traffic light features (neurological symptoms, non-blanching rash) [11]. A complete case analysis was also performed.

Discrimination plots were used to compare the predicted risks for bacterial pneumonia and for other SBIs for each outcome category [29].

To quantify the ability to discriminate between bacterial pneumonia, other SBIs and no SBI, the pairwise C-statistic (equal to the area under the receiver operating curve AUC) was calculated for pairs of outcomes (pneumonia and no SBI, and other SBI and no SBI) [29]. The polytomous discrimination index (PDI) [30], where the lower bound for PDI is $1/(Number\ of\ outcomes)$, was also calculated.

Model calibration, which describes the agreement between the predicted risks and observed number of events, is important for models intended to inform decision-making. To assess calibration, the predicted risks of pneumonia were compared with the observed proportions of pneumonia and the predicted risks of other SBIs were compared with the observed proportions of other SBIs. Calibration intercept (ideally 0) and slope (ideally 1) were reported and flexible calibration curves were plotted [31].

Diagnostic performance (sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios) was assessed for risk thresholds between 1% and 30% for children with bacterial pneumonia compared with all others (children with other SBIs and with no SBI) and for children with other SBIs compared with all others (children with pneumonia and with no SBI).

Model update

The model was updated by re-fitting a polytomous multivariable prediction model to this cohort using the *Feverkids* variables (Appendix 2). The model was then further developed by incorporating other variables of clinical interest: neutropenia with neutrophils <0.5 x 10^9/L and NICE red traffic light features (neurological symptoms, non-blanching rash) [11] and by exploring the effect of restricting

other SBIs to only those with invasive bacterial infection (IBI), those with isolation of pathogenic bacteria from blood, cerebrospinal fluid, or synovial fluid [23].

Results

Population characteristics

Of 592 episodes, 31 episodes were excluded as they did not have a minimum of two clinical model predictor variables and three patients with a final diagnosis of a parasitic infection were also excluded. 558 episodes were included following imputation of missing values. There were 21 cases of bacterial pneumonia (3.8%), 104 cases of other SBI (18.8%) and 433 cases of no SBI. The recommended number of events needed to update the *Feverkids* model was calculated at n=59 for bacterial pneumonia and n=71 for other SBIs [27].

Table 1 describes the participant characteristics.

Table 1 - Participant characteristics: Predictor variables, underlying diagnosis causing immunocompromise, other characteristics and interventions and outcome for each group

	Bacterial pneumonia (n=21)	Other SBI (n=104)	No SBI (n=433)
Predictor variables			
Age (years)	7.4 (4.9-12.8)	9.0 (4.0-13.7)	7.8 (4.4-12.7)
Male sex	16 (76%)	61 (59%)	250 (58%)
Temperature on admission (ºC)	37.4 (37.1-37.9)	38.3 (37.1-39.1)	38.0 (37.2-38.4)
Missing values n (%)	*0 (0%)*	*2 (2%)*	*6 (1%)*
Tachycardia	12 (57%)	55 (53%)	200 (47%)
Missing values n (%)	*2 (10%)*	*6 (6%)*	*23 (5%)*
Tachypnoea	14 (67%)	24 (23%)	134 (31%)
Missing values n (%)	*3 (14%)*	*30 (29%)*	*85 (20%)*
Oxygen saturations <94%	6 (33%)	0 (0%)	31 (8.6%)
Missing values n (%)	*2 (10%)*	*14 (14%)*	*68 (16%)*
Capillary refill >3 seconds	2 (10%)	5 (6%)	7 (2%)
Missing values n (%)	*1 (5%)*	*15 (14%)*	*99 (23%)*
Ill appearance	11 (55%)	49 (48%)	106 (27%)
Missing values n (%)	*1 (5%)*	*1 (1%)*	*40 (9%)*
Chest wall recessions	6 (29%)	2 (2%)	20 (5%)
Duration of illness (days)	2 (0-3)	0 (0-1)	0 (0-2)
C-reactive protein (mg/L)	182 (47-225)	36 (16-88)	21 (6-53)
Missing values n (%)	*0 (0%)*	*1 (1%)*	*10 (2%)*
Underlying diagnosis n (%)			
Haematological malignancy	4 (20%)	35 (34%)	168 (39%)

Central nervous system malignancy	0 (0%)	7 (7%)	26 (6%)
Other solid organ malignancy	2 (10%)	12 (12%)	72 (17%)
Non-malignant haematological disease	8 (38%)	8 (8%)	52 (12%)
Inflammatory syndrome	1 (5%)	5 (5%)	41 (9%)
Primary immunodeficiency	1 (5%)	6 (6%)	39 (9%)
Cystic fibrosis	1 (5%)	1 (1%)	3 (0.7%)
Solid organ transplant	3 (14%)	14 (13%)	13 (3%)
Human immunodeficiency virus infection	0 (0%)	5 (5%)	1 (0.2%)
Nephrotic syndrome	0 (0%)	3 (3%)	3 (0.7%)
Short bowel syndrome	0 (0%)	2 (2%)	2 (0.5%)
Other conditions	1 (5%)	6 (6%)	13 (3%)
Other characteristics			
Receiving chemotherapy	5 (24%)	48 (46%)	242 (56%)
Receiving other immunosuppressant drugs	12 (57%)	59 (57%)	233 (54%)
Neutropenia <0.5 x 10^9/L	4 (19%)	38 (37%)	188 (43%)
Interventions and outcome			
Empirical antibiotics started	20 (95%)	102 (98%)	349 (81%)
Admitted to PICU	10 (48%)	10 (10%)	31 (7%)
Died	2 (10%)	1 (1%)	8 (2%)

Data are presented as n (%) or median (IQR). SBI: Serious Bacterial Infection. PICU: Paediatric Intensive Care Unit. The number and percentage of missing values are reported for variables which were imputed.

Table 2 details the source of other SBIs.

Table 2 - Source of other serious bacterial infections

Source of other SBIs	n=104 (%)
Bacteraemia (CLABSI)	34 (33%)
Bacteraemia (other)	13 (13%)
Cellulitis	7 (7%)
Gastroenteritis/colitis	6 (%)
Meningitis	5 (5%)
Surgical (intra-abdominal, abscess, wound infection)	13 (13%)
URTI	5 (5%)
UTI/pyelonephritis	18 (17%)
Other	3 (2%)

CLABSI: Central line associated blood stream infection SSI: Surgical site infection URTI: Upper respiratory tract infection UTI: Urinary tract infection

The most common aetiology was central line associated blood stream infection (CLABSI) (n=34). 59 other SBIs had invasive bacterial infection (IBI), of which 58 had a positive blood culture and one had a positive cerebrospinal fluid culture.

Of 433 patients with no SBI, 70 had a probable viral illness and 55 had a definite viral illness confirmed with a positive viral PCR. Non-infectious causes of illness included adverse effects of treatment for malignancy or haematopoietic transplant and inflammatory conditions. 116 (27%) of those with no SBI had a chest radiograph and 349 (81%) received empirical antibiotics.

Validation of the original prediction model

Figure 1 shows discrimination plots comparing the predicted risks of bacterial pneumonia (a) and other SBI (b) for each outcome category. The *Feverkids* tool showed good external validity for prediction of bacterial pneumonia, with area under the curve (AUC) 0.83 (95% CI: 0.74-0.93) (Figure 2a). The AUC for other SBI prediction was 0.67 (0.61-0.72) (Figure 2b). The polytomous discrimination index of the model was 0.55 (0.48-0.63).

A complete case analysis (n=323) showed AUC for bacterial pneumonia prediction (n=16) was 0.81 (0.68-0.95) and the AUC for other SBI prediction (n=64) was 0.63 (0.56-0.71).

Model calibration

Calibration curves for the prediction of bacterial pneumonia and other SBIs are shown in Figure 3. The calibration for bacterial pneumonia was good, with slope 0.93 (95% CI 0.59-1.27) and intercept -0.54 (95% CI -1.01-0.08). Calibration for prediction of other SBIs was poorer, with slope 0.36 (0.23-0.49) and intercept 1.00 (0.75-1.25).

Model update

The re-fitted model (Appendix 2) showed improved AUC for bacterial pneumonia of 0.88 (95% CI 0.79-0.96) and 0.71 (0.65-0.76) for other SBIs (Figure 4). The PDI improved to 0.65 (0.59-0.76) and calibration of both models improved (Figure 5).

The addition of the variables neutropenia (<0.5 x 10^9/L), neurological signs and non-blanching rash did not significantly improve the AUC for bacterial pneumonia (0.88 (0.75-0.95)) or other SBIs (0.72 (0.67-0.78)). Restricting the other SBI category to only those with IBI (n=59) resulted in a model with similar performance, with AUC for prediction of pneumonia of 0.88 (0.76-0.95) and for other IBIs of 0.69 (0.62-0.75).

Diagnostic thresholds

The dichotomous diagnostic performance measures for bacterial pneumonia and other SBIs at different risk thresholds for the re-fitted model are detailed in Table 3.

Table 3 – Dichotomous diagnostic performance measures for pneumonia and other SBIs at different risk thresholds in the re-fitted model

	% above/below threshold	Sensitivity (95% CI)	Specificity (95% CI)	Predictive value (95% CI)		Likelihood ratio (95% CI)	
				Positive	Negative	Positive	Negative
Pneumonia							
1.0% *	51/49	0.95 (0.86-1.00)	0.53 (0.48-0.58)	0.09 (0.08-0.10)	1.00 (0.99-1.00)	2.00 (1.71-2.27)	0.09 0.00-0.32
2.5%	31/69	0.86 (0.67-1.00)	0.71 (0.67-0.76)	0.13 (0.10-0.15)	0.99 (0.98-1.00)	2.99 (2.27-3.67)	0.20 0.02-0.45
5%	17/83	0.71 (0.52-0.90)	0.85 (0.82-0.88)	0.19 (0.13-0.25)	0.98 (0.97-0.99)	4.75 (3.18-6.62)	0.34 0.12-0.58
10%**	11/89	0.57 (0.38-0.76)	0.91 (0.88-0.94)	0.24 (0.16-0.33)	0.98 (0.97-0.99)	6.51 (3.71-10.3)	0.47 0.25-0.71
15%	6/94	0.57 (0.38-0.76)	0.96 (0.94-0.97)	0.39 (0.26-0.54)	0.98 (0.97-0.99)	13.0 (7.01-23.8)	0.45 0.24-0.67
Other SBI							
2.5%	97/3	1.00 (1.00-1.00)	0.03 (0.01-0.04)	0.20 (0.20-0.20)	1.00 (1.00-1.00)	1.02 (1.00-1.04)	0.00 (0.00-1.23)
5%	92/8	0.99 (0.97-1.00)	0.09 (0.07-0.12)	0.21 (0.20-0.21)	0.98 (0.92-1.00)	1.09 (1.05-1.13)	0.10 (0.00-0.40)
10%*	78/22	0.92 (0.87-0.97)	0.24 (0.20-0.28)	0.23 (0.21-0.24)	0.93 (0.88-0.97)	1.22 (1.12-1.31)	0.32 (0.13-0.57)
15%	59/41	0.84 (0.76-0.90)	0.45 (0.40-0.50)	0.27 (0.24-0.29)	0.92 (0.89-0.95)	1.52 (1.34-1.71)	0.36 (0.21-0.54)
30%**	15/85	0.32 (0.23-0.40)	0.89 (0.86-0.92)	0.41 (0.31-0.50)	0.84 (0.83-0.86)	2.86 (1.91-4.25)	0.77 (0.66-0.87)

*Possible rule-out threshold ** Possible rule-in threshold

Low-risk rule-out thresholds were identified, where a clinician might reasonably stop workup. 49% of participants had a predicted risk of bacterial pneumonia ≤1%. This low-risk threshold ruled out bacterial pneumonia with sensitivity of 0.95 (95% CI 0.86-1.00) and negative likelihood ratio (LR) of 0.09 (0.00-0.32).

22% of participants had a predicted risk of SBI of ≤10%. This low-risk threshold ruled out other SBIs with sensitivity of 0.92 (0.87-0.97) and negative LR of 0.32 (0.13-0.57).

11% of participants were above a high-risk threshold of 10% for bacterial pneumonia, which identified bacterial pneumonia with specificity of 0.91 (0.88-0.94) and positive LR of 6.51 (3.71-10.3). 15% of participants were above a high-risk threshold of 30% for other SBIs, which identified other SBIs with specificity 0.89 (0.86-0.92) and positive LR of 2.86 (1.91-4.25).

Discussion

Interpretation and clinical implications

This study assesses the external validity of the *Feverkids* tool in a heterogeneous group of immunocompromised children.

The discriminative ability of the model to predict bacterial pneumonia in this cohort was good, with performance comparable to the derivation and external validation cohorts of healthy children [8] and with adequate calibration.

The discriminative ability of the model to predict other SBIs in this study was poorer than in the derivation cohort (AUC 0.86) but comparable to the external validation cohort (AUC 0.69) [8]. This may be due to differences in case mix: bacterial pneumonia and UTI were the most common SBIs in the original study, and in this cohort, central line-associated bloodstream infection (CLABSI) was the most common cause of SBI. This population has a higher prevalence of inflammatory conditions which mimic the clinical features of infection, which contributed to the poorer performance of the predictive tool for other SBIs. Importantly, the higher rate of SBI in this cohort limits the utility of the model, as it systematically under-estimated the risk of other SBIs. This improved with re-fitting.

Concerns about missing SBIs in immunocompromised children may contribute to over-investigation and treatment. The identification of low-risk thresholds adds to work on using the *Feverkids* tool to limit unnecessary clinical investigations and antimicrobial overuse [32, 33]. For example, in the no SBI group, 116 participants had a chest radiograph. If clinicians did not perform a chest radiograph in participants with <1% bacterial pneumonia risk, 49 fewer participants with no SBI would have been X-rayed, a reduction of 42%. Estimating the reduction in empirical antibiotic usage is more challenging as it depends on understanding the rationale for initiating antibiotic treatment in each patient.

The calibrated low-risk threshold for other SBIs in this study (10%) is significantly higher than in the original study (<2.5%) [8], however no established risk thresholds exist in this population, and a 10% low-risk threshold is in keeping with another study in febrile neutropenia [19].

Strengths and Limitations

This is the largest cohort of its kind to date, with well-characterised cases representing diverse underlying causes for immunodeficiency, recruited from multiple centres and countries across Europe. However, the study has fewer than the recommended number of cases of bacterial pneumonia to update the *Feverkids* prediction model, which demonstrates the challenge of gathering large cohorts of patients of this type. Multiple imputation of missing values improved the study precision [34] and complete case analysis showed similar results to the imputed dataset.

The heterogeneity of the study population reflects the case mix and across Europe and permits wider application and generalisability of the results. Participants were only recruited at academic/tertiary care hospitals, nonetheless this reflects that most care provided to this population is supported with specialist guidance. There was insufficient power to undertake site-specific analyses.

This study uses the original study's classification into three outcome categories and does not assess the ability to predict specific SBIs, although the exploratory model for IBI performed similarly. The heterogeneity of other SBIs in this study may have limited the predictive ability of the model.

Further work

Immunocompromised children may present with severe illness with or without a bacterial aetiology, therefore predictive tools may be limited in their ability to distinguish serious bacterial infections by clinical features alone. The prediction model uses CRP as the only laboratory variable. Future predictive models may benefit from using biomarkers such as interleukin-6, interleukin-8, interleukin-10, and TNFα [36] in conjunction with clinical features.

Conclusions

This study validates a prediction model using clinical features and CRP for identification of bacterial pneumonia and other SBI in children with immunodeficiency presenting with febrile illness or suspected infection. The model shows good discrimination and calibration for bacterial pneumonia and poorer discrimination and calibration for other SBIs. There is a need for predictive tools to identify serious bacterial infections in immunocompromised children. Tools combining clinical features, established markers of infection and novel biomarkers are likely needed to improve the diagnosis of serious bacterial infection in this group.

Post-conclusions text:

Authors' contributions

AJM wrote the original manuscript, performed the statistical analysis and contributed to preparing the database and recruitment. FvdV reviewed the manuscript and was responsible for the study dataset and data quality control. GdV was involved in the preparation of the database and patient recruitment. UvB, MT, WZ, CV, LK, EL, MP, DZ, FMT, IRC, NH, EU, LS, TK, AP, SY, CF, MV, EC, PA, AK, SP, JH, ML, MvdF, RdG, RN and ME were responsible for the conduct of the PERFORM study and patient recruitment for their respective sites. TD was responsible for the digital database system and its maintenance. RN and ME supervised the project. All authors reviewed and approved the final manuscript.

Ethical approval

Ethical approval was obtained in all participating countries via their national ethics committees (for the UK: IRAS: 209035, REC: 16/LO/1684). Informed consent was obtained from all participants or their legal guardians with assent from older children.

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What is already known on this topic:

1. Most febrile children without pre-existing comorbidities have viral illnesses, however immunocompromised children are at an increased risk of infection with bacterial and viral pathogens.
2. Existing clinical prediction tools to differentiate viral and bacterial illnesses have mostly been developed in children with no underlying conditions.

What this study adds

1. This study is a validation of an existing clinical prediction tool for bacterial pneumonia and other serious bacterial infections in a population of immunocompromised children.
2. The tool, combining clinical features and CRP, had good discrimination and calibration for bacterial pneumonia, however discrimination and calibration for other SBIs was poorer.

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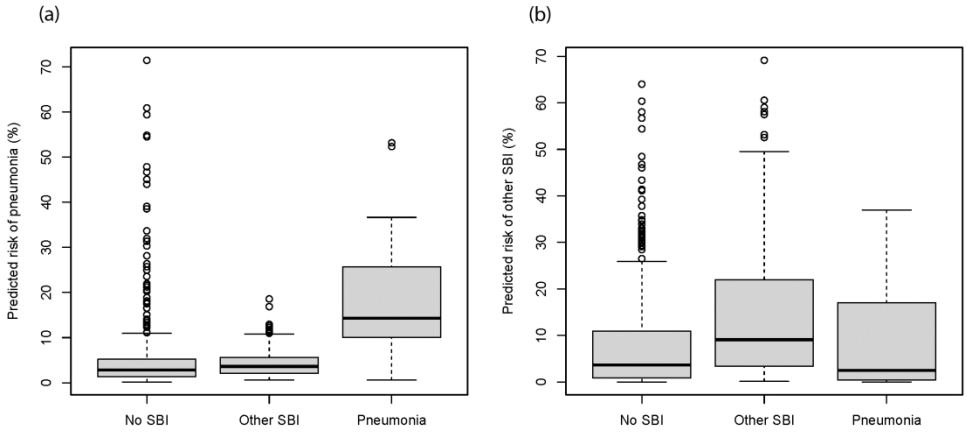

Figure 1 - Discrimination plot of Feverkids model prediction score for bacterial pneumonia (a) and Feverkids model prediction score for other SBIs (b) for no SBI, other SBI and bacterial pneumonia groups

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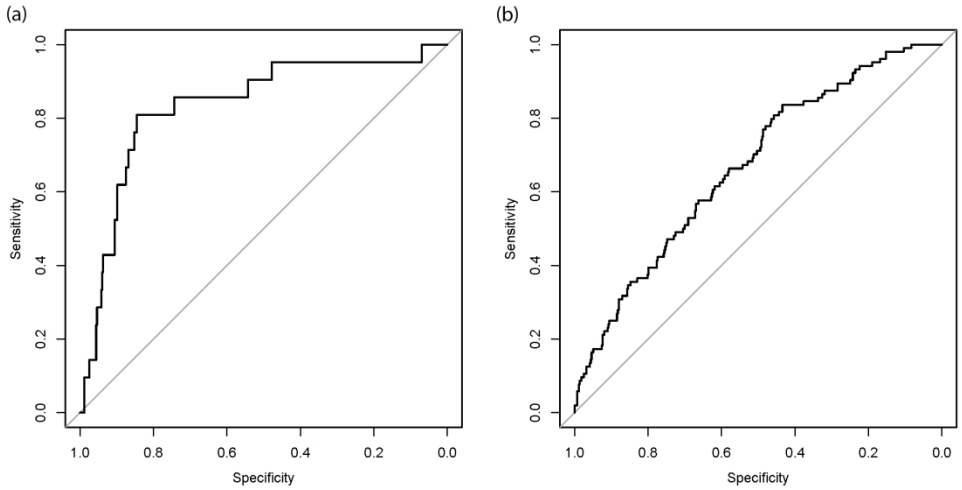

Figure 2 – Dichotomous ROC curve for discrimination of bacterial pneumonia versus no SBI (a) and other SBI versus no SBI (b) for the original Feverkids model

771x385mm (79 x 79 DPI)

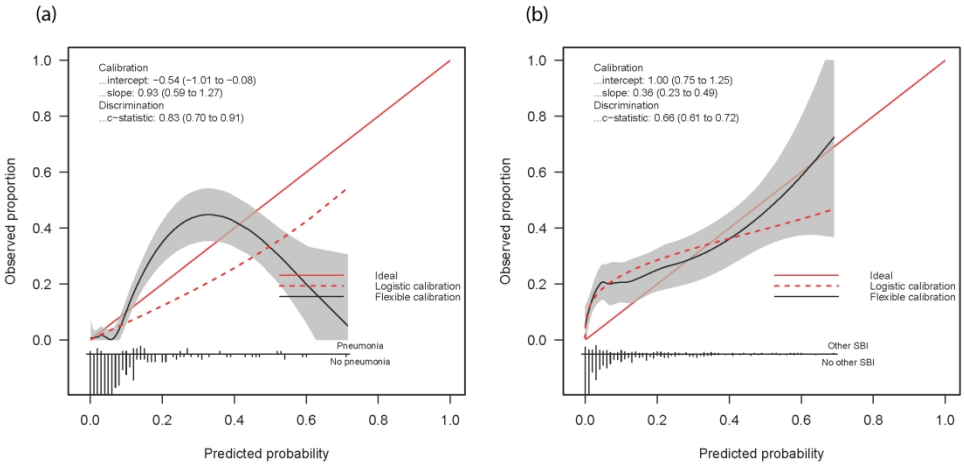

Figure 3 - Calibration plot of predicted risks of pneumonia (a) and other SBIs (b) against observed frequencies for the original Feverkids model. Red diagonal line represents ideal calibration. Distribution of predicted risks of patients with outcome is shown at bottom of graph.

771x385mm (79 x 79 DPI)

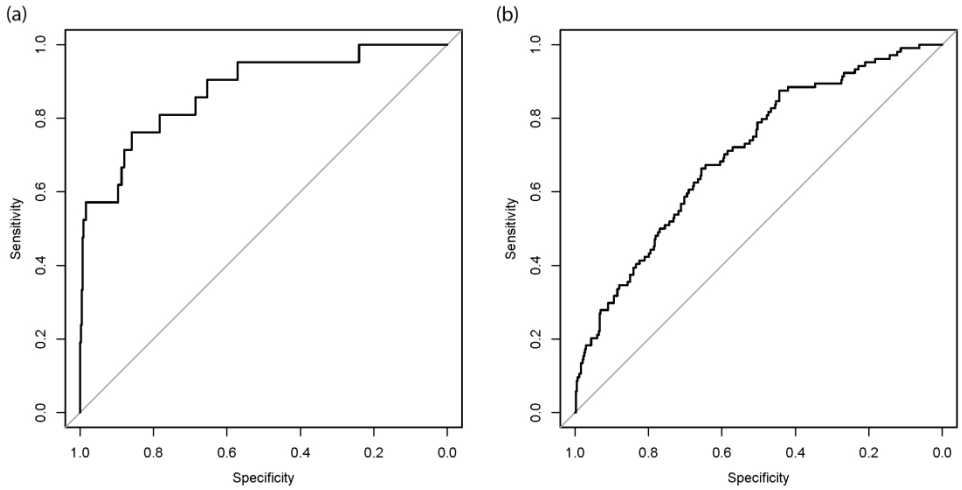

Figure 4 - Dichotomous ROC curve for discrimination of bacterial pneumonia versus no SBI (a), other SBI versus no SBI (b) for the re-fitted model

771x385mm (79 x 79 DPI)

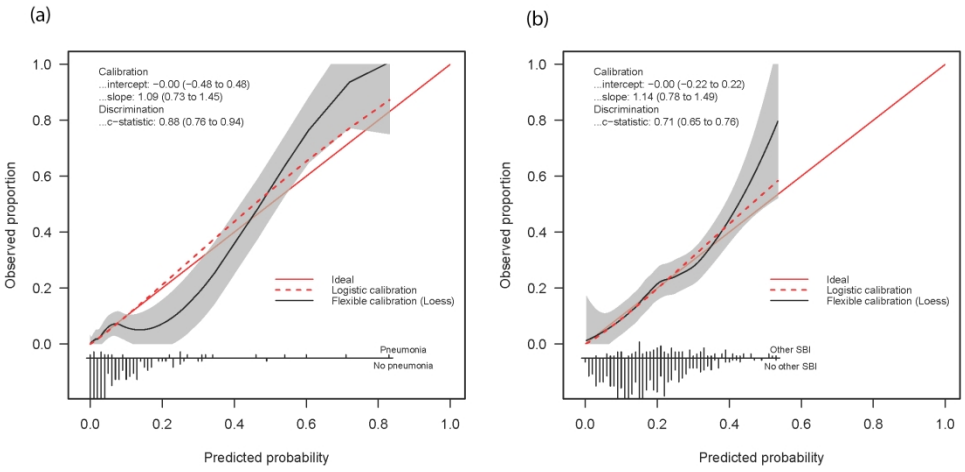

Figure 5 - Calibration plot of predicted risks of pneumonia (a) and other SBIs (b) against observed frequencies for the re-fitted model. Red diagonal line represents ideal calibration. Distribution of predicted risks of patients with outcome is shown at bottom of graph.

771x385mm (79 x 79 DPI)

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TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	5
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6
	5c	D;V	Give details of treatments received, if relevant.	NA
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	-
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	7
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	D;V	Explain how the study size was arrived at.	7
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	7
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	7
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	8
	10c	V	For validation, describe how the predictions were calculated.	7
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	8
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	8
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	8
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	14
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	9
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	9
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	9
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	9
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	NA
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	App 2
	15b	D	Explain how to the use the prediction model.	14
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	11
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	11
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	15
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	14
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	14
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	14
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	App 2
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	16

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

Reference: Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement. BMC medicine. 2015;13:1.

Appendix 2

Probabilities of the outcomes are calculated with:

$$Risk_{(P)} = \frac{e^{LP_{(P)}}}{(1 + e^{LP_{(P)}} + e^{LP_{(S)}})}$$

$$Risk_{(S)} = \frac{e^{LP_{(S)}}}{(1 + e^{LP_{(P)}} + e^{LP_{(S)}})}$$

Where $LP_{(P)}$ is the linear predictor in a (polytomous) logistic regression model for pneumonia and $LP_{(S)}$ for other SBIs.

The coefficients for the original logistic regression model are:

$$LP_{(P)} = -17.9 + 1.02A_1 + 0.01A_2 + 0.13S + 0.29T + 0.21D + 0.44T_P - 0.04T_C + 1.59O_2 - 0.18C + 0.47R + 0.16I + 0.64\text{Ln(CRP)}$$

$$LP_{(S)} = -4.7 + -1.73A_1 + 0.11A_2 + 0.7S - 0.02T - 0.03D - 0.11T_P - 0.02T_C - 3.29O_2 + 0.30C - 3.78R + 0.27I + 1.14\text{Ln(CRP)}$$

The coefficients for the re-fitted model are:

$$LP_{(P)} = 0.98 + -0.04A_1 + 20.8A_2 - 0.89S - 0.78T + 0.08D + 1.02T_P + 0.79T_C + 0.47O_2 - 0.41C + 1.07R + 0.81I + 0.93\text{Ln(CRP)}$$

$$LP_{(S)} = -5.9 + 0.02A_1 - 0.69A_2 + 0.14S + 0.10T - 0.13D - 0.26T_P + 0.08T_C - 40O_2 - 0.36C - 0.89R + 1.02I + 0.43\text{Ln(CRP)}$$

$$A_1 = \begin{cases} 1 & \text{if age } > 1 \text{ year} \\ \text{Age (years)} & \text{if age } \leq 1 \text{ year} \end{cases}$$

$$A_2 = \begin{cases} \text{Age (years)} - 1 & \text{if age } > 1 \text{ year} \\ 0 & \text{if age } \leq 1 \text{ year} \end{cases}$$

$$S = \begin{cases} 1 & \text{if female} \\ 0 & \text{if male} \end{cases}$$

T = Temperature (ºC)

D = Duration of fever (days, maximum 6)

$$T_P = \begin{cases} 1 & \text{if tachypnoeic} \\ 0 & \text{if not tachypnoeic} \end{cases}$$

$$T_C = \begin{cases} 1 & \text{if tachycardic} \\ 0 & \text{if not tachycardic} \end{cases}$$

$$O_2 = \begin{cases} 1 & \text{if oxygen saturations } < 94\% \\ 0 & \text{if oxygen saturations } \geq 94\% \end{cases}$$

$$C = \begin{cases} 1 & \text{if capillary refill time } > 3 \text{ seconds} \\ 0 & \text{if capillary refill time } \leq 3 \text{ seconds} \end{cases}$$

$$R = \begin{cases} 1 & \text{if chest wall recessions present} \\ 0 & \text{if no chest wall recessions present} \end{cases}$$

$$I = \begin{cases} 1 & \text{if ill appearance} \\ 0 & \text{if not ill appearance} \end{cases}$$

CRP measured in units $\mathrm{mg/l}$

References

1 Begg CB, Gray R. Calculation of polychotomous logistic-regression parameters using individualized regressions. Biometrika 1984;71:11-8.

2 Wijesinha A, Begg CB, Funkenstein HH, McNeil BJ. Methodology for the differential diagnosis of a complex data set. A case study using data from routine CT scan examinations. Med Decis Making 1983;3:133-54

3 Nijman RG, Vergouwe Y, Thompson M, van Veen M, van Meurs AHJ, van der Lei J, et al. Clinical prediction model to aid emergency doctors managing febrile children at risk of serious bacterial infections: diagnostic study. BMJ : British Medical Journal. 2013;346:f1706.