A MODEL COMBINING PROCALCITONIN, C-REACTIVE PROTEIN AND URINALYSIS IS SUPERIOR TO INDEPENDENT VARIABLES FOR PREDICTING SERIOUS BACTERIAL INFECTIONS IN FEBRILE CHILDREN

Diana A. Moldovan[1,2], Maria D. Baghiu[1,3], Cristian Boeriu

Abstract

Introduction and aim. Fever is a common complaint for children addressing the emergency departments (ED). Distinguishing between febrile children with self limited viral infection and those with serious bacterial infection (SBI) may be challenging for practitioners, especially in younger population. Recently, a laboratory score, named the Lab-score, combining Procalcitonin, C-reactive protein and urine dipstick was developed for predicting SBI in febrile children. The Lab-score was further assessed and validated in several studies. We aimed to search current literature and evaluate its value per se and by comparison with independent variables. ***Method.*** We search electronically the literature, in Medline, Embase and Google Scholar and identified the articles directly related to the Lab-score. We analysed the results of each study selected and corroborated the data. ***Results.*** The search returned 773 articles, six of them being relevant for the study. The highest sensitivity for the Lab-score for predicting SBI was 94% (95%CI: 82-99) and the highest specificity was 95% (95%CI: 93-96). The highest performance found for the Lab-score was reflected by an AUC of 0.91 (95%CI: 0.87-0.93) and the lowest by an AUC of 0.73 (95%CI: 0.69-0.77). We found that in four studies the Lab-score performed significantly better than independent predictors associated with SBI. Two studies found similar prediction power comparing the Lab-score with independent variables, one assessing a small group of infants and one assessing a much broader age group than all other studies. ***Conclusions.*** The Lab-score is a valuable tool for predicting SBI in febrile children addressing to ED and superior to independent variables, particularly in younger groups. Further validations are required for stronger conclusions.

Key words: fever, children, C-reactive protein, Procalcitonin, Lab-score

Introduction

Fever, one of the main reasons children are brought in emergency settings1,2, has always been a concern for practitioners, especially when related to serious bacterial infections (SBI) such as urinary tract infection (UTI), pneumonia, bacteraemia, meningitis, sepsis. Particularly in young children, who often have fever without an apparent focus3, distinguishing between a self limited viral infection and an SBI may be challenging.

Diagnosis of SBI in febrile children, which was reported to be around 20%4, has been researched during the past years in relation with new biomarkers. Among many proposed, C-reactive protein and Procalcitonin proved strong prediction value in detecting SBI5-14. Recently, a laboratory index score, named the "Lab-score", combining PCT, CRP and urinalysis showed promising results for identifying SBI in children younger than 36 months with fever without source15. The Lab-score has already been assessed and validated in several studies16-20.

We aimed to assess the value of the Lab-score in identifying SBI in febrile children and whether the Lab-score performs better than independent biomarkers, namely PCT and CRP, by reviewing the existing literature on the subject.

Methods

The Lab-score was developed in 2008 by Galetto-Lacour et al15, and combines PCT, CRP and urine dipstick which were the only independent predictors contributing to a stepwise multiple logistic regression model predicting SBI in febrile children. According to the Lab-score, 0 points are attributed for PCT<0.5ng/ml, 2 points for PCT ≥0,05ng/ml and 4 points for PCT ≥2ng/ml; also 0 points are attributed if CRP is <40mg/l, 2 points if CRP value ranges between 40mg/l and 99mg/l and 4 points for CRP ≥100mg/l. 1 point is attributed for positive urine dipstick, that is if positive leukocyte esterase and/or nitrates. The Lab-score values range from 0 to 9, and the cut-off of ≥3 points was proposed as optimal for SBI prediction.

[1] University of Medicine and Pharmacy Tirgu Mures, Department of Paediatrics Tirgu Mures, Romania
[2] Tirgu Mures Emergency Clinical County Hospital, Emergency Department Tirgu Mures, Romania
[3] Tirgu Mures Emergency Clinical Hospital, Paediatric Unit
[4] University of Medicine and Pharmacy Tirgu Mures, Department of Intensive Care and Emergency Medicine
E-mail: diana.moldovan@fundatiapentrusmurd.ro, baghiumaria@rocketmail.com, cboeriu@gmail.com

Table 1. General characteristics of analysed studies

Study	Design	Number of participants	SBI (%)	Age range	Inclusion criteria	Outcome diagnosis
Galetto-Lacour, 2008[15]	Prospective, observational	202	27	7days-36months	Temperature (rectal) >38.0°C and without localising signs of infection in history or at physical examination	Bacteraemia, UTI, lobar pneumonia, meningitis, osteoarthritis
Galetto-Lacour, 2010[16]	Prospective, observational	406	22,7	7days-36months	Temperature (rectal) >38.0°C (7days-3months) and without localising signs of infection in history or at physical examination and temperature (rectal) >39,5^{0}C (3-36months) or toxic appearing	Bacteraemia, UTI, lobar pneumonia, meningitis, osteoarthritis, sepsis
Bressan, 2012[17]*	Retrospective	1012	28,3	less than 3 months	Fever (axillary or rectal) without localizing signs of infection	UTI, bacterial gastroenteritis
		1098	2,1	less than 3 months	Fever without localizing signs of infection	UTI and bacteraemia, occult bacteraemia, meningitis
Nijman, 2014[18]	Prospective, observational	1084	16	1month-16years	Temperature (rectal)>38,5^{0}C	Bacteraemia, UTI, lobar pneumonia, meningitis, osteoarthritis, osteomyelitis, cellullitis orbitae, erysipelas, bacterial gastroenteritis
Lacroix, 2014[19]	Randomized controlled trial	271	24,7	7days-36months	Temperature >38.0°C and without localising signs of infection in history or at physical examination	Bacteraemia, UTI, lobar pneumonia, meningitis, osteoarthritis, bacterial gastroenteritis
Moldovan, 2015[20]	Prospective, observational	90	21,1	7days-12months	Temperature >38.0°C and without localising signs of infection in history or at physical examination	Bacteraemia, UTI, lobar pneumonia, meningitis, bacterial gastroenteritis, sepsis

SBI: serious bacterial infection

*Bressan et al[17] dichotomized sever infections in SBI and IBI (invasive bacterial infections). The authors included 1012 infants for SBI analysis and 1084 infants for IBI analysis. UTI and bacterial gastroenteritis were defined as SBI and occult bacteraemia, UTI and bacteraemia and meningitis were defined as IBI.

Table 2. Diagnostic value of CRP, PCT and the Lab-score for SBI

Parameter	Cut-off value	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR -(95%CI)
CRP					
Galetto-Lacour, 2008[15]	40	**81 (65-90)**	76 (67-83)	n.a.	n.a.
Galetto-Lacour, 2010[16]	40	73 (63-81)	81 (77-85)	3.8 (3.0-5.0)	**0.34 (0.24-0.47)**
Bressan, 2012[17]	n.a.	n.a.	n.a.	n.a.	n.a.
Nijman, 2014[18]	40	58 (50-65)	81 (78-83)	2.98 (2.47-3.58)	0.53 (0.44-0.63)
Lacroix, 2014[19]	n.a.	n.a.	n.a.	n.a	n.a.
Moldovan, 2015[20]	40	57 (33-79)	**94 (86-98)**	**10.27 (3.68-29)**	0.45 (0.26-0.76)
PCT					
Galetto-Lacour, 2008[15]	0,5	**94 (82-99)**	68 (58-76)	n.a.	n.a.
Galetto-Lacour, 2010[16]	0,5	75 (65-83)	76 (71-81)	3.1 (2.5-4.0)	0.33 (0.23-0.47)
Bressan, 2012[17]	n.a.	n.a.	n.a.	n.a.	n.a.
Nijman, 2014[18]	0,5	60 (52-67)	78 (75-81)	2.73 (2.29-3.24)	0.51 (0.43-0.62)
Lacroix, 2014[19]	n.a.	n.a.	n.a.	n.a.	n.a.
Moldovan, 2015[20]	0,5	78 (54-93)	**88 (78-95)**	**7.01 (3.50-14)**	**0.24 (0.10-0.57)**
Lab-score					
Galetto-Lacour, 2008[15]	3	**94 (82-99)**	81 (72-88)	4.92 (3.26-7.43)	**0.07 (0.02-0.27)**
Galetto-Lacour, 2010[16]	3	86 (77-92)	83 (79-87)	5.1 (3.9-5.5)	0.17 (0.1-0.28)
Bressan, 2012[17]	3	52 (46-58)	**95 (93-96)**	**10.2 (9.5-10.9)**	0.5 (0.5-0.5)
Nijman, 2014[18]	3	60 (52-67)	86 (84-88)	4.32 (3.53-5.29)	0.46 (0.39-0.56)
Lacroix, 2014[19]	3	85 (76-93)	87 (82-91)	6.68 (n.a.)	0.17 (n.a.)
Moldovan, 2015[20]	3	73 (48-90)	92 (84-97)	**10.43 (4.39-25)**	0.28 (0.13-0.6)

CRP: C-reactive protein, PCT: procalcitonin,; LR: likelihood ratio; n.a.: not available

Table 3. Area under the receiver operating characteristic curves for CRP, PCT and the Lab-score for SBI prediction reported in the analysed studies

Parameter	AUC (95%CI)
CRP	
Galetto-Lacour, 2010[16]	**0.86 (0.82-0.89)**
Bressan, 2012[17]	0.77 (0.73-0.80)
Nijman, 2014[18]	0.77 (0.69-0.85)
Lacroix, 2014[19]	0.83 (0.77-0.89)
PCT	
Galetto-Lacour, 2010[16]	**0.84 (0.80-0.87)**
Bressan, 2012[17]	0.73 (0.69-0.77)
Nijman, 2014[18]	0.75 (0.67-0.83)
Lacroix, 2014[19]	0.81 (0.75-0.87)
Lab-score	
Galetto-Lacour, 2010[16]	**0.91 (0.87-0.93)**
Bressan, 2012[17]	0.83 (0.80-0.86)
Nijman, 2014[18]	0.79 (0.72-0.87)
Lacroix, 2014[19]	**0.91 (0.87-0.95)**

CRP: C-reactive protein, PCT: procalcitonin,;
AUC: area under the receiver operating characteristic curve

We searched the literature electronically, in Medline, Embase and Google Scholar, using the key words associated with serious infections, fever, children, laboratory scores, emergency department. Studies were selected if they assessed the Lab-score value in predicting SBI in children, aged less than 16 years, with fever with or without a source. SBI were defined as UTI, pneumonia, bacteraemia, sepsis, meningitis, bacterial gastroenteritis, cellulitis, septic arthritis and osteomyelitis.

Results

The electronic search in Medline, Embase and Google Scholar, using the key words mentioned above in the Method paragraph, returned nearly 773 results, although, refining the search, we found only six articles directly relevant for our study. Besides the study which proposed the Lab-score, we found two studies which validated the original score, two studies which assessed the new method and one clinical trial which assessed the impact of the Lab-score on antibiotic prescription rate. The final number of studies analysed was six, comprising 3151 patients. The general characteristics of included studied are reported in Table 1.

All studies were carried in the emergency department. Except for one study17 which was retrospective, all studies enrolled patients prospectively. Presence of fever was an inclusion criterion for all studies. Five studies included children with fever without localizing signs of infection. One single study included children with fever with or without signs of infection, although excluded those patients with fever and a clear focus of an upper airway infection, considering them as having a very low risk of SBI.18 Three studies included children between 7 days and 36 months of age,15,16,19 one study infants less than 3 months17, one study infants less than 12 months20 and one study children between 1 month and 16 years.18 The outcome diagnosis of SBI included bacteraemia, UTI, pneumonia, meningitis (six studies), osteoarthritis (four studies), sepsis (two studies), osteomyelitis, cellullitis orbitae, erysipelas (one study). For the six studies analysed the prevalence of SBI ranged between 16% and 28,3%.

All studies included for analysis had CRP, PCT and urinalysis taken from all patients and the Lab-score calculated. In Table2 are reported the sensitivities, specificities and positive and negative likelihood ratio for the CRP, PCT and the Lab-score as found in the studies included in the analysis. The best sensitivity obtained for the Lab-score was 94% (95%CI: 82-99)15 and the best specificity was 95% (95%CI: 93-93)17.

Analysing the area under the receiver operating characteristic curve (AUC) we found better performance for the Lab-score in comparison with CRP and PCT in the analysed studies, where it was available (Table3).

Discussion

Structured approach and step wise decision making are of paramount importance for identification of children having serious conditions, as well as for safe discharge of those with minor illnesses, in EDs with increasing overcrowding. Recently, practitioners have taken the challenge to develop tools for identifying SBI in febrile children presenting in EDs by using the new surrogate biomarkers, especially CRP and PCT.15,21

The Lab-score, proposed by Galetto-Lacour et al15 in 2008, showed promising results and was already assessed and validated in several studies. The original study included two cohorts of children with fever without a source (FWS) prospectively enrolled from the same hospital, in Geneva, Switzerland. 202 children, age 7 days to 36 month, were analysed. The derivation population comprised 135 children and the validation population 67 children. 54 children (27%) from 202, had SBI. The performance of the Lab score was robust and similar in both populations with sensitivities of 94% (derivation set) and 94% (validation set) and specificities of 81% (derivation set) and 78% (validation set) at a cut-off value of $\geq$3.15 A systematic review published by Van den Bruel et al4 argued that from 14 studies assessing the value of laboratory tests for identifying SBI in febrile children, the Lab-score offered the best prediction rule for the purpose.

In 2010 the Lab score was externally validated on a cohort of 406 children with FWS age 7 days to 36 months from Padua, Italy.16 The performance of the Lab-score was similar (86% sensitivity and 83% specificity) and also better than for independent variables associated with SBI. The study supports the use of the Lab-score in clinical practice for identifying febrile children at risk for SBI, instead of the old models which included white blood cell count (WBC) which proved poor prediction for SBI. Nevertheless, recent data suggest that WBC should not be used currently as triage tool for febrile children for distinguishing between viral and bacterial disease.22

Bressan et al17 assessed the method on a retrospective study including 1098 infants less than 3 months, with FWS, from five Spanish and two Italian pediatric EDs. The population was analysed for SBI and IBI. A lower sensitivity for the Lab-score for SBI prediction was obtained by comparison with the original study. However, the authors proposed, in order to increase the sensitivity, lower CRP cut-off values and higher scores for PCT values between 0.5 and 2ng/ml. Fever duration was also proposed to be taken into consideration. However, the Lab-score proved significantly superior to independent variables for SBI prediction.

Nonetheless, Nijman et al21 , proposing a clinical prediction model which included the added value of CRP, as well as fever duration, offered a promising alternative for identification of SBI in febrile children. The model offered risk thresholds rather than a single cut-off level. In another study, Nijman et al18 also validated externally the Lab-score and proposed an updated model. The population included, comprising 1084 febrile children age 1 month to 16 years, was recruited from a university hospital's ED, from Rotterdam, The Netherlands. However, the results were intriguing, CRP and the Lab-score having a similar performance in predicting SBI, and both slightly higher than PCT. Nevertheless, as the authors argued, the population differed in age limits and this could interfere the results. The

updated model only modestly outperformed the original Lab-score. In addition, the same authors suggested a step-wise approach of febrile children, an idea also argued by Mintegi et al23 in a study on febrile young infants (less than 3 months).

We also performed a study in Tirgu Mures, Romania, in a university hospital's ED, assessing infants (less than 12 months) with FWS for SBI.20 We found robust performance for the Lab-score, but only slightly superior to CRP. However, the group study was rather small to make a definitive conclusion.

A randomized clinical trial, performed in the same center where the Lab-score was developed, assessed the impact of the Lab-score on the antibiotic prescription rate in children with FWS, age 7 days to 36 months.19 Testing the Lab-score prospectively was the second objective of the study. The Lab-score performed better than any other independent biomarker for SBI detection. The investigators argued that if the Lab-score would have been strictly used, a significant 26.5% reduction of antibiotic prescription rate would have been encountered.

From the six studies analysed there is evidence that the Lab-score is a valuable tool for identifying SBI in febrile children and superior to independent variables associated with SBI. It might be wiser though, to limit its use particularly in infants and young children with FWS, for whom the Lab-score was designed and who are more prone for SBI. The strength of the method is given by its easy-to-use pattern, while the cost of two biomarkers, PCT being more expensive, makes it less affordable for poor resource settings.

The main limitation of our study consists in the rather small number of studies included for analysis. Further external validations are required to draw more robust conclusions.

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Correspondence to:

Diana A. Moldovan
Tirgu Mures Emergency Clinical County Hospital
Emergency Department.
Gh. Marinescu Street, No. 50,
Tirgu Mures, 540136, Romania
Phone: +40265210110
E-mail: diana.moldovan@fundatiapentrusmurd.ro