



Original Contribution

C-reactive protein or erythrocyte sedimentation rate results reliably exclude invasive bacterial infections



Niloufar Paydar-Darian*, Amir A. Kimia, Michael C. Monuteaux, Kenneth A. Michelson, Assaf Landschaft, Alexandra B. Maulden, Rachel L. Chenard, Lise E. Nigrovic

Division of Emergency Medicine, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115, USA

ARTICLE INFO

Article history:

Received 16 May 2018

Received in revised form 2 October 2018

Accepted 6 November 2018

Keywords:

Erythrocyte sedimentation rate

C-reactive protein

Fever

Invasive bacterial infection

ABSTRACT

Background: Clinicians utilize inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), to identify febrile children who may have an occult serious illness or infection.

Objectives: Our objective was to determine the relationship between invasive bacterial infections (IBIs) and CRP and ESR in febrile children.

Methods: We performed a retrospective cross-sectional study of 1460 febrile children <21 years of age, who presented to a single Emergency Department (ED) between 2012 and 2014 for evaluation of fever of <14 days' duration, who had both CRP and ESR obtained. Our primary outcome was IBI, defined as growth of pathogenic bacteria from a culture of cerebrospinal fluid or blood. We reviewed all ED encounters that occurred within three days of the index visits for development of IBI. We examined the negative predictive value (NPV) of CRP and ESR for IBI.

Results: Of the 1460 eligible ED encounters, the median patient age was 5.3 years [interquartile range (IQR) 2.4–10.0 years] and 762 (50.4%) were hospitalized. The median duration of fever was 4 days (IQR 1–7 days). Overall, 20 had an IBI (20/1460; 1.4%, 95% confidence interval (CI) 0.9–2.1%). None of those with a normal CRP (NPV 273/273; 100%, 95% CI 98.6–100%) or a normal ESR (NPV 486/486; 100%, 95% CI 99.2–100%) had an IBI.

Conclusions: In our cross-sectional study of febrile children, IBI was unlikely with either a normal CRP or ESR. Inflammatory markers could be used to assist clinical decision-making while awaiting results of bacterial cultures.

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1. Introduction

While most febrile children presenting to the emergency department (ED) have self-limited viral infections [1], a small but important proportion have an invasive bacterial infection (IBI), such as bacteremia or meningitis, that requires prompt identification and initiation of appropriate therapy to avoid morbidity and mortality [2]. Alongside the clinical history and examination, clinicians frequently utilize diagnostic testing to identify children at the highest risk [3–5].

C-reactive protein (CRP) is an acute phase protein produced by the liver in response to inflammation, which binds to surfaces of dead or dying bacteria in order to activate the complement system. The erythrocyte sedimentation rate (ESR), the distance that red blood cells (RBCs)

travel in 1 h, increases with systemic inflammation because acute phase reactants cause erythrocyte stacking, thereby increasing the velocity of RBC sedimentation. Together, CRP and ESR are inflammatory markers that ED clinicians measure to assess the likelihood of an infectious or inflammatory disorder.

The ability of CRP and ESR to reliably exclude an IBI has not been previously examined in the ED setting. To this end, we identified febrile children <21 years presenting to a single pediatric ED whose treating clinician obtained both a CRP and ESR during the ED visit. Our primary aim was to determine the ability of CRP and ESR to reliably exclude IBI in otherwise healthy children presenting to the ED for evaluation of fever.

2. Materials and methods

2.1. Study design

We performed a retrospective cross-sectional study of children with fever who presented to a single pediatric ED over the three-year period from January 2012 through December 2014. The study protocol was

* Corresponding author.

E-mail addresses: niloufar.paydar-darian@childrens.harvard.edu (N. Paydar-Darian), Amir.Kimia@childrens.harvard.edu (A.A. Kimia), Michael.Monuteaux@childrens.harvard.edu (M.C. Monuteaux), Kenneth.Michelson@childrens.harvard.edu (K.A. Michelson), landschaft@fastmail.fm (A. Landschaft), Alexandra.Maulden@childrens.harvard.edu (A.B. Maulden), Rachel.Chenard@childrens.harvard.edu (R.L. Chenard), lise.nigrovic@childrens.harvard.edu (L.E. Nigrovic).

approved by the institutional review board at our institution with a waiver of informed consent.

2.2. Patient population

We identified ED encounters for febrile children <21 years of age in which the treating clinician obtained both CRP and ESR during the index encounter. The decision to obtain inflammatory markers was at the discretion of the treating provider and was not included in departmental fever algorithms. If a patient had more than one encounter within seven days, the initial eligible encounter was selected. Children with more than one eligible ED encounter more than seven days apart could be included more than once.

We included children with a measured fever at home or in the ED of ≥ 38.0 °C of <14 days' duration due to differential approach to prolonged fevers. We excluded ED encounters for children with any of the following: chronic medical conditions (e.g. inflammatory bowel disease, cystic fibrosis, cardiac or renal disease, periodic fever syndrome or malignancy), immune deficiency (inherited or acquired), critical illness (altered mental status, hypotension requiring vasoactive infusions, or assisted ventilation), or surgery within the previous two months.

2.3. Case identification

Our case identification method consisted of several phases. We utilized a natural language processing tool (Dr. T™) which uses regular-expression matching to build an automated case identification tool [6,7]. First, we built a training set consisting of potentially eligible ED encounters from a single study year (2014). We then manually screened each of these documents to determine whether the identified ED encounter met all inclusion criteria and none of the exclusion criteria. Our manual review was used to build a document classifier to further identify eligible encounters. Next, we refined the automated tool using an iterative process [8,9]. ED encounters identified by the classifier were assigned a likelihood score for study eligibility, and then manually reviewed to determine study status. This process was used repeatedly to improve the performance of the automated tool until the sensitivity reached was >92%. We applied the final classifier to the remaining ED records and considered the case identification process saturated when the ratio of ineligible to eligible cases reached 10:1.

2.4. Data abstraction

The following data elements were abstracted automatically from the electronic data warehouse: age, sex, race, ethnicity, insurance status (private or public), laboratory studies (including CRP and ESR), triage temperature, discharge diagnoses, and ED disposition (discharge versus admission). We reviewed whether the patient had been referred to the study ED by another provider, as these children tended to have higher severity of illness. From our manual medical record review, we determined whether the study patient had been pretreated with antibiotics, which we defined as any antibiotic administered within the three days before the index encounter. We also reviewed all repeat ED encounters within three days after the index encounter to determine if the child developed bacteremia or bacterial meningitis.

We also utilized a previously developed natural language processing tool to abstract duration of fever from the ED medical record. First, we manually reviewed a random selection of approximately 10% of potentially eligible ED encounters ($N = 278$) and abstracted fever duration. We then applied this automated fever duration tool to the same ED encounters and measured the agreement between the manual and automated fever duration: weighted kappa statistic of 0.85 (95% confidence interval (CI): 0.80–0.89). Given the excellent agreement, we utilized this automated tool to determine fever duration for each of the remaining ED encounters [10,11]. ED encounters missing fever duration after application of the automated tool were manually

reviewed (<5% of encounters). Given the challenges in accurately determining exact fever duration for children with a longer duration of illnesses from existing medical records, we grouped those with a fever duration of more than one week together (i.e. days 8 to 13 of fever duration).

2.5. Predictors

Our main predictors were the two inflammatory markers, CRP and ESR, obtained during the initial ED encounter. We utilized our institution's laboratory cut-points to classify test results as normal: CRP ≤ 0.5 mg/dL and ESR ≤ 20 mm/h. For CRP results that were below the level of assay detection, we imputed a value of one half the lower level of detection.

2.6. Outcome measure

Our primary outcome was IBI, defined as growth of pathogenic bacteria from either blood or cerebrospinal (CSF) culture. We assumed that children who did not have a blood or CSF culture obtained but who did not return within three days of the index encounter with bacteremia or meningitis did not have an IBI. Bacterial cultures that grew more than one species were considered contaminated unless one or more species was classified as a pathogen. Normal skin and oral flora were defined a-priori as contaminants.

2.7. Statistical analysis

First, we described the patient population compared proportions using Chi Square and medians using the Mann Whitney test.

We then explored the relationship between fever duration and both CRP and ESR using a box plot to depict distribution. Next, to compare the rate of change of CRP and ESR by day of fever compared to the first day, we used a general linear model with a log-transformed dependent variable alone and after adjustment for patient age, sex, race, insurance status (public vs. private), referral status (referred vs. not referred) and antibiotic pretreatment (yes vs. no). We tested the hypothesis that ESR lags CRP in rise and fall by comparing the mean percent change in CRP to that of ESR by day of fever after adjustment for covariates.

Finally, we examined the ability of CRP and ESR to reliably exclude IBI (primary outcome). To this end, we examined the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of CRP and ESR for IBI.

We utilized both the Statistical Program for the Social Sciences (SPSS) version 22.0 (IBM Corporation; Armonk, NY) as well as Stata version 13.0 (StataCorp LP; College Station, TX) for statistical analyses.

3. Results

3.1. Patient encounters

Of the 166,208 ED encounters to the study institution over the study period, we identified 1460 eligible ED encounters (0.9% of all ED encounters) (Fig. 1). Of the 1332 visits with ED discharge diagnosis codes available, 788 (59.2%) had fever as either the primary or secondary ED discharge or admission diagnostic code.

Of the 1460 eligible ED encounters, the median age was 5.3 years [interquartile range (IQR) 2.4–10.0 years] and only three study patients were <90 days of age. Half of the children were referred by another provider and half were hospitalized (Table 1). Although most children presented with a fever with non-specific symptoms, other associated symptoms included cough, limp, headache, suspected soft tissue infection, adenitis, and rash.

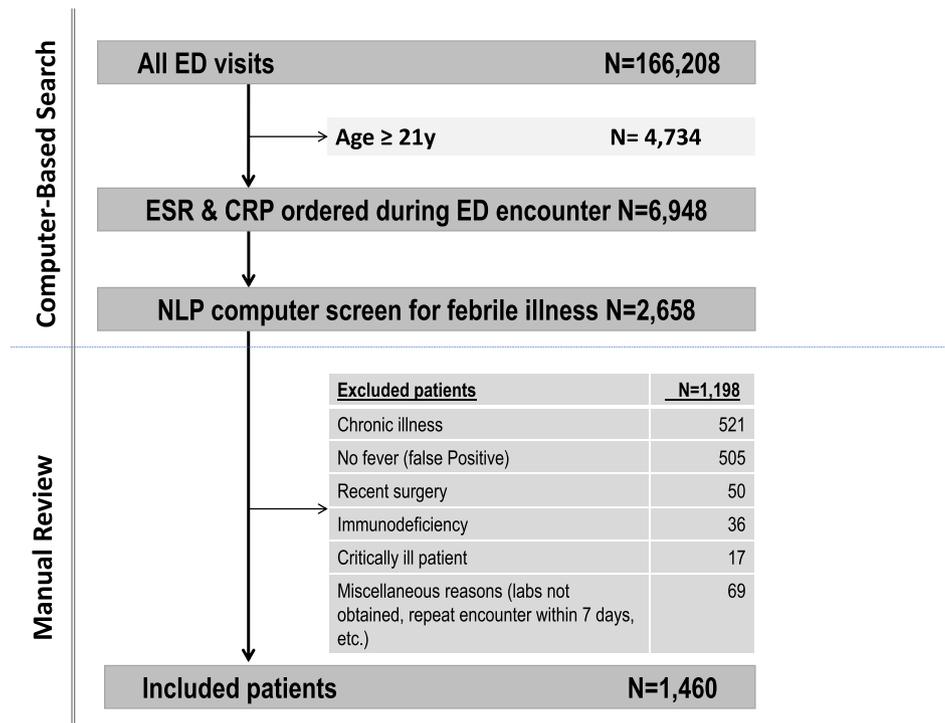


Fig. 1. Patient population flow diagram.

3.2. Inflammatory markers

Of the eligible ED encounters, 273 (18.7%; CI 16.8–20.8%) had a normal CRP, 486 (33.3%; 95% CI 30.9–35.8%) had a normal ESR, and 200 (13.7%; 95% CI 12.0–15.6%) had both. Children who had been pretreated with antibiotics had a higher median CRP (3.2 mg/dL pretreated, IQR 1.0–7.5 mg/dL vs. 2.8 mg/dL not pretreated, IQR 0.7–6.7 mg/dL; $p = 0.03$) and a higher median ESR (36 mm/h pretreated, IQR 20–64 mm/h vs. 30 mm/h not pretreated, IQR 14–53 mm/h; $p \leq 0.001$).

3.3. Relationship of ESR and CRP with duration of fever

First, we present the median CRP and ESR by duration of fever at the time of presentation (Fig. 2). Using linear regression, CRP did not but ESR did increase with each additional day of fever (CRP: β 0.01 mg/dL,

Table 1
Patient characteristics for eligible ED encounters.

Category	n/N (%) (N = 1460)	95% CI (%)
Age ^a (years)	5.3	[2.4–10.0]
Sex (male)	774/1460 (53.0%)	[50.5, 55.6]
Race		
White	763/1358 (56.2%)	[53.5, 58.8]
Black	160/1358 (11.8%)	[10.2, 13.6]
Asian	99/1358 (7.3%)	[6.0, 8.8]
Other	336/1358 (24.7%)	[22.5, 27.1]
Ethnicity		
Hispanic	279/1267 (22.0%)	[19.8, 24.4]
Non-Hispanic	988/1267 (78.0%)	[75.6, 80.2]
Insurance		
Public	554/1454 (38.1%)	[35.6, 40.6]
Private	900/1454 (61.9%)	[59.4, 64.4]
Antibiotic pretreatment	439/1460 (30.1%)	[27.8, 32.5]
Referred to the ED	734/1460 (50.3%)	[47.7, 52.8]
Triage temp ≥ 39 °C	224/1459 (15.4%)	[13.6, 17.3]
Hospitalized	743/1452 (51.2%)	[48.6, 53.7]

^a Median [interquartile range].

95% CI -0.02 – 0.04 mg/dL; ESR: β 0.47 mm/h, 95% CI 0.29–0.44 mm/h). We then compared the mean percent changes in CRP and ESR with each additional day of fever relative to children presenting on day one of fever. After adjustment for patient demographics and clinical covariates, the mean percent changes for both CRP and ESR by day of fever were similar (Fig. 3).

3.4. Bacterial infections

The majority of included encounters had a blood culture obtained ($n = 1013$; 69.4%) while only a small minority had a CSF culture ($n = 28$; 1.9%). Of those with a blood culture obtained, 20 (2.0%; 95% CI 1.3–3.0%) had bacteremia and, of those with a CSF culture, none had bacterial meningitis (0%; 95% CI 0–12%). Of those with bacteremia, the following pathogens were isolated: *Staphylococcus aureus* ($n = 14$), *Streptococcus pneumoniae* ($n = 2$), *Salmonella enteritidis* ($n = 2$), and *Streptococcus pyogenes* ($n = 2$). Forty-seven of the children (3.2%) returned within three days of the initial encounter and one child had persistent bacteremia. This two-year old male had initially presented with fever and hip pain and was discharged home with a CRP of 4.05 mg/dL and an ESR of 27 mm/h. He was called back to the ED within 24 h when his initial blood culture became positive. Both the initial and follow-up cultures grew *Streptococcus pyogenes* and the child was diagnosed with femoral osteomyelitis. Overall, 20 children had an IBI (20/1460; 1.4%, 95% CI 0.9–2.1%).

Of the 20 children with an IBI, the median CRP was 6.7 mg/dL (IQR 4.3–14.6 mg/dL) and ESR was 39 mm/h (IQR 28–74 mm/h). The median duration of fever for children with an IBI was 3 days (IQR 1–6 days). None of the 20 children with an IBI had either a normal CRP or ESR (Table 2).

4. Discussion

We assembled a large cross-sectional sample of children presenting to a single pediatric ED over a three-year period for the evaluation of a febrile illness, who had inflammatory markers (i.e. CRP and ESR) obtained by the treating clinician. Both commonly obtained inflammatory

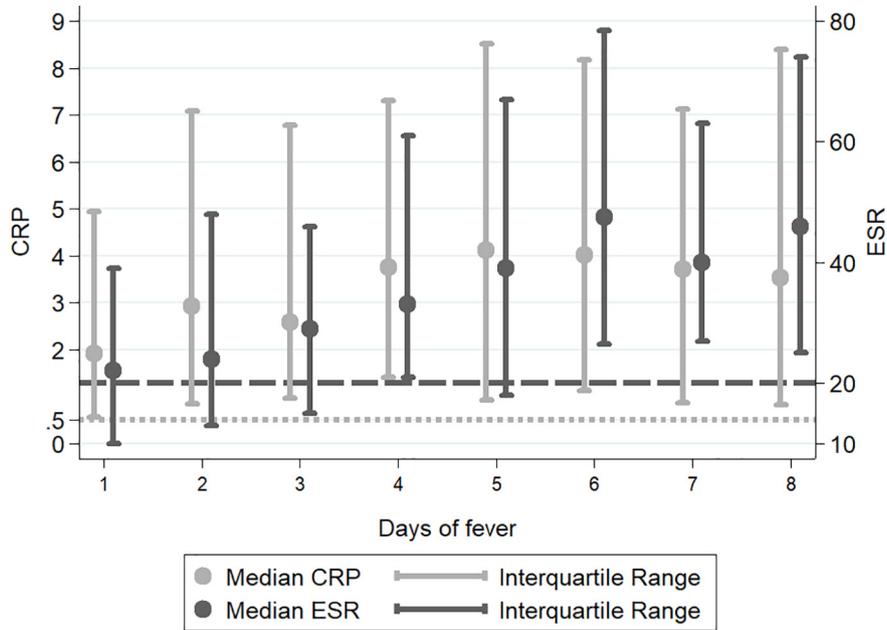


Fig. 2. Median CRP and ESR with interquartile range by day of fever. The upper limits of normal (CRP of 0.5 mg/dL and ESR of 20 mm/h) have been drawn as a dotted reference line.

markers increased with longer fever duration. None of the children with an IBI had either a normal CRP or ESR result, suggesting these tests could be used to reliably exclude IBI before results of bacterial culture become available.

The challenge for clinicians is that most previously healthy febrile children have viral infections, although a minority may have invasive bacterial infections or other serious conditions that require prompt identification and initiation of appropriate therapy. Inflammatory markers can assist clinical decision-making by risk-stratifying patients in advance of diagnostic tests, such as cultures which may take several days to result [5]. Several small ED studies have found CRP and procalcitonin to be predictive of serious bacterial infections, but have been limited by small sample size and heterogeneity of study population [13–19]. A prospective European cohort study that included 1084 previously healthy children with one day or less of fever, found both

CRP and procalcitonin to be only a minimally accurate predictor of a serious bacterial infection [area under receiver operating characteristic curve for CRP of 0.77 (95% CI 0.69–0.85) and for procalcitonin of 0.75 (95% CI 0.67–0.83)] [20,21]. In our larger retrospective study, we found that either a normal CRP or ESR could reliably exclude IBI and might assist initial clinical decision-making.

Previous longitudinal studies have examined changes in inflammatory markers over time, with each patient having markers obtained multiple times over the course of illness. Small pediatric studies have demonstrated that CRP begins to rise within 4 to 6 h after onset of inflammation or acute tissue injury, doubling every 8 h. In these studies, CRP peaked at 36–50 h, then returned to normal within 3 to 7 days with resolution of inflammation. In contrast, ESR rises gradually, reaching a peak up to one week after the inflammatory or traumatic stimulus, taking up to several weeks to return to normal [22]. The

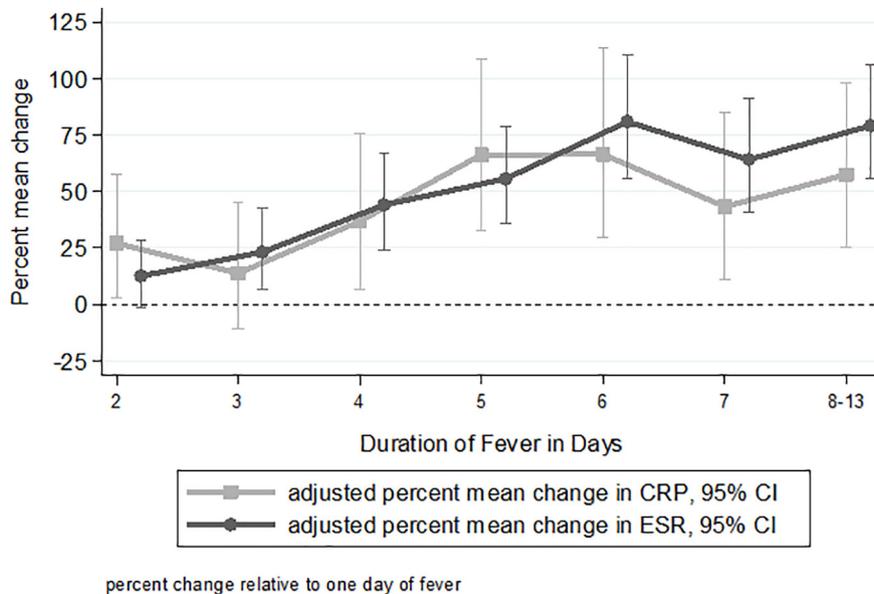


Fig. 3. Mean percent change in CRP vs. ESR compared to those who present on day one of fever, adjusted for patient age, sex, insurance status, antibiotic pre-treatment, triage temperature, and referral status.

Table 2

Test performance of CRP > 0.5 and ESR > 20 for the diagnosis of invasive bacterial infections.

	CRP > 0.5 mg/dL n/N % (95% CI)	ESR > 20 mm/h n/N % (95% CI)
Sensitivity	20/20 100% (83.9, 100)	20/20 100% (83.9, 100)
Specificity	273/1440 19% (17.0, 21.1)	486/1440 33.8% (31.4, 36.2)
NPV	273/273 100% (98.6, 100)	486/486 100% (99.2, 100)
PPV	20/1187 1.7% (1.1, 2.6)	20/974 2.1% (1.3, 3.2)

time course of inflammatory marker elevation has also been investigated in rheumatologic disorders [23–26], post-operative conditions [27,28], and inflammatory bowel disease [29,30]. Variation in both study population and sampling strategy across studies precludes applicability of these results to our study population of previously healthy children presenting to the ED for evaluation of fever.

Our study differs from previous studies in several important ways. First, we chose to exclude children with critical illness or clinically significant comorbidities, which can complicate the interpretation of inflammatory markers as well as influence subsequent clinical management. Second, we were unable to compare the predictive ability of CRP or ESR to procalcitonin. At the study institution, procalcitonin was rarely obtained by treating clinicians as results did not return in a clinically relevant time-frame. Third, our study allowed comparison between inflammatory markers by day of fever at the time of ED evaluation but not over time for the same patient. Acute care providers rarely have the opportunity to follow disease courses over time, and must make initial diagnostic, therapeutic and management decisions based on the available clinical and laboratory assessments. In addition, we used a novel natural language processing tool to identify cases, which increased the accuracy of case identification given the limitations of discharge diagnostic codes [31].

Our study provides additional insights into the interpretation of inflammatory markers as part of the diagnostic evaluation for febrile children. By rigorously examining the pattern of elevation in both CRP and ESR relative to the duration of fever, we provided a broader context for clinical interpretation. Importantly, most study patients had both elevated CRP and ESR. Additionally, given the simultaneous rise in CRP and ESR coupled with the more rapid turn-around time for CRP results, clinicians could consider ordering CRP alone when evaluating febrile children. Overall, the rate of bacterial infections was very low. In fact, all of the children with either an IBI or an SBI had both elevated CRP and ESR, regardless of fever duration. In the appropriate clinical scenario (i.e. a low pre-test probability of IBI), clinicians could consider using a normal CRP and ESR to “rule-out” an IBI while awaiting final bacterial culture results.

Our study had several limitations. First, our study was conducted in a single pediatric referral center. We chose to exclude children with critical illness or clinically significant comorbidities, which can complicate the interpretation of inflammatory markers as well as influence subsequent clinical management. However, our findings may not be generalizable to other clinical settings [32]. Second, we built and applied a novel computerized natural-language processing tool for case identification with an iterative process for tool refinement. Although we estimate that few eligible ED encounters were missed by this tool, more than one third of the eligible encounters would have been missed if we relied on ED discharge diagnoses codes alone. Third, our study was retrospective and relied on existing medical records although we selected objective clinical factors and laboratory results to minimize recording biases. Fourth, we utilized an existing automated tool to facilitate the abstraction of fever duration from the record. However, the agreement

between our manual and automated abstraction process was quite high. Importantly, we abstracted the duration of the most recent fever documented, but some children may have had another recent illness, which could impact their inflammatory marker results. Fifth, we were limited to febrile children whose treating clinician ordered inflammatory markers, with considerable inter-provider variability in test-ordering and no specific algorithms to guide test ordering. The high hospital admission rate suggests that clinicians tested children with a higher severity of illness or a longer duration of symptoms. As our study included very few young infants, our findings should not be applied to neonates being evaluated for bacterial infections who may not have ESR or CRP obtained as part of routine evaluation. Sixth, we did not exclude children who had been pretreated with any antibiotics which could have rendered bacterial cultures falsely negative. Seventh, not all children had a blood or CSF bacterial culture obtained. However, we examined all repeat ED encounters within three days to identify children who were later diagnosed with an IBI. Although we cannot exclude the possibility that children who had an unrecognized IBI returned to a different hospital, we believe that this occurred rarely as the study ED serves as the regional pediatric referral center [33]. Eighth, our study had only a small number of children with invasive bacterial infections and no children with bacterial meningitis, limiting the precision in our point estimates. However, in the conjugate vaccine era, this reflects the clinical reality [34,35]. Last, given our cross-sectional design, we were unable to examine trends in these markers over time for a single patient. Future longitudinal cohort studies are needed to explore these questions.

4.1. Conclusions

In conclusion, in our sample of previously healthy children presenting to a pediatric ED for evaluation of fever, both CRP and ESR levels increased with longer fever duration. Inflammatory markers may help clinicians risk stratify febrile children by reliably excluding IBI while awaiting final bacterial culture results.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

None.

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