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ORIGINAL PAPER

Using the kinetics of C-reactive protein response to improve the differential diagnosis between acute bacterial and viral infections

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Abstract

Purpose Differential diagnosis between acute viral and bacterial infection is an emerging common challenge for a physician in the emergency department. Serum C-reactive protein (CRP) is used to support diagnosis of bacterial infection, but in patients admitted with low CRP, its ability to discriminate between viral and bacterial infections is limited. We aimed to use two consecutive CRP measurements in order to improve differential diagnosis between bacterial and viral infection.

Methods A single-center retrospective cohort ($n = 1629$) study of adult patients admitted to the emergency department with a subsequent microbiological confirmation of either viral or bacterial infection. Trend of CRP was defined as the absolute difference between the first two measurements of CRP divided by the time between them, and we investigated the ability of this parameter to differentiate between viral and bacterial infection.

Results In patients with relatively low initial CRP concentration (< 60 mg/L, $n = 634$ patients), where the uncertainty regarding the type of infection is the highest, the trend improved diagnosis accuracy (AUC 0.83 compared to 0.57 for the first CRP measurement). Trend values above 3.47 mg/L/h discriminated bacterial from viral infection with 93.8% specificity and 50% sensitivity.

Conclusions The proposed approach for using the kinetics of CRP in patients whose first CRP measurement is low can assist in differential diagnosis between acute bacterial and viral infection.

Keywords Bacterial · Viral · C-reactive protein · Differential diagnosis · Infection

Background

One of the main challenges facing physicians on a daily basis is to accurately distinguish between bacterial and viral infections [1], which is crucial in deciding on antibiotic treatment and institution of sepsis protocols. Misdiagnosis leads to overuse and misuse of these medications, which contribute to the antibiotic resistance crisis [2, 3], increase care costs and can lead to adverse events [4]. Misdiagnosis or delayed diagnosis also may increase mortality of bacterial sepsis, in which very early institution of protocolized care is critical. Traditional techniques used to distinguish between types of infection depend on laboratory technologies that generally

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aim to identify the pathogen itself and are therefore slow, labor intensive and expensive. Recently, it was suggested that immune response proteins could be used as an indicator of the infection type [5, 6].

C-reactive protein (CRP) is an acute phase protein, a well-known biomarker for inflammatory response. Even though bacterial infections are associated with higher concentrations of CRP, it was reported to have limited utility for the detection of a microbial etiology [7]. Several studies tried to find the optimal cutoff for probable bacterial infection, where CRP concentration above that cutoff would positively identify bacterial infection and lower concentration would imply an uncertain diagnosis. Suggested cutoffs included 10 mg/L [8], 20 mg/L [9], 60 mg/L [10, 11], 75 mg/L [12] and 100 mg/L [13, 14]. The lower cutoffs present high sensitivity but poor specificity, whereas higher cutoffs present low sensitivity and high specificity. While an exact cutoff is disputable, it is clear that lower concentrations of CRP are indicative of both bacterial and viral infections. This highlights the patients presenting with low CRP levels as a group with the most uncertainty [15]. Moreover, this subgroup represents a substantial fraction of the patients admitted to the emergency department [16]. Hence, improving the prediction on this subgroup can have an important clinical impact [17, 18].

Our hypothesis was that the dynamics of CRP levels could represent the severity of inflammatory response, and thus can play an essential role in the diagnostics of etiology and distinguish between viral and bacterial infection, especially in patients admitted with low CRP. We hypothesized that such distinction could be particularly beneficial for this subgroup of patients, where bacterial infection is less probable than in those with very high CRP, and the dynamics of CRP could thus be more revealing.

Previous studies reported the use of serial CRP measurements up to 5 days in patients with blood-stream infection or sepsis [19–23]. However, these studies mainly focused on the usefulness of CRP as a surrogate of response to therapy [24, 25] or as post-operative [26, 27], rather than on etiology prospects.

In this study, we propose to use the kinetics of CRP, based on the first two measurements following the admission to the hospital, in order to differentiate between viral and bacterial infection.

Methods

Study design and setting

We conducted a retrospective cohort study comprising all patients admitted to the Emergency Department (ED) in Tel Aviv Medical Sourasky Center, Israel, between January 2012 and December 2016 who had at least two CRP tests and a later positive lab test that indicated an infection. Our study was based only on electronic medical record (EMR) data and covered 3665 adult patients (aged ≥ 18) and was reviewed and approved by the Institutional Review Board (number 0491-17).

Patients

Inclusion criteria

Bacterial infections were identified by a positive bacterial blood culture ($n=2539$). Viral infections were identified by either a positive PCR for a virus or an Immunoglobulin test indicative of acute viral infection ($n=1126$). If a patient was admitted to the ED multiple times, we included only the first admission.

Exclusion criteria

Patients who had a positive viral test and a discharge diagnosis of a potentially bacterial infection such as cellulitis, cholecystitis, erysipelas, pneumonia, pyelonephritis or septicemia, which may suggest cross-contamination ($n=34$). Patients with a positive viral test and a positive bacterial blood culture ($n=35$). Patients who had more than one type of virus ($n=1$), or more than one bacterial species ($n=0$). Patients with positive blood cultures for bacteria that were likely to be contaminants and not a true infection (defined as blood culture results of *Diphtheroids* spp, coagulase-negative *Staphylococcus*, *Staphylococcus haemolyticus*, *Streptococcus viridans* group and a result of Gram-positive bacilli) ($n=322$). Patients with time difference between the first two CRP measurements greater than 24 h ($n=1251$). And patients whose blood culture or PCR/immunoglobulin test was taken more than 1 day (bacterial) or 5 days (viral) before or after the first CRP measurement ($n=358$) (Fig. 1).

After applying these criteria, our *general cohort* included 1629 patients (589 viral and 1040 bacterial). The subgroup of patients from the general cohort with the first CRP measurement (CRP1) <60 mg/L was called the *low-CRP1 group* ($n=634$; 369 viral, 265 bacterial).

Laboratory methods

Wide range (WR) CRP measurements were done by ADVIA 2400, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA. The ADVIA® Chemistry. The WR-CRP method measures CRP in the serum and plasma by a latex-enhanced immunoturbidimetric assay.

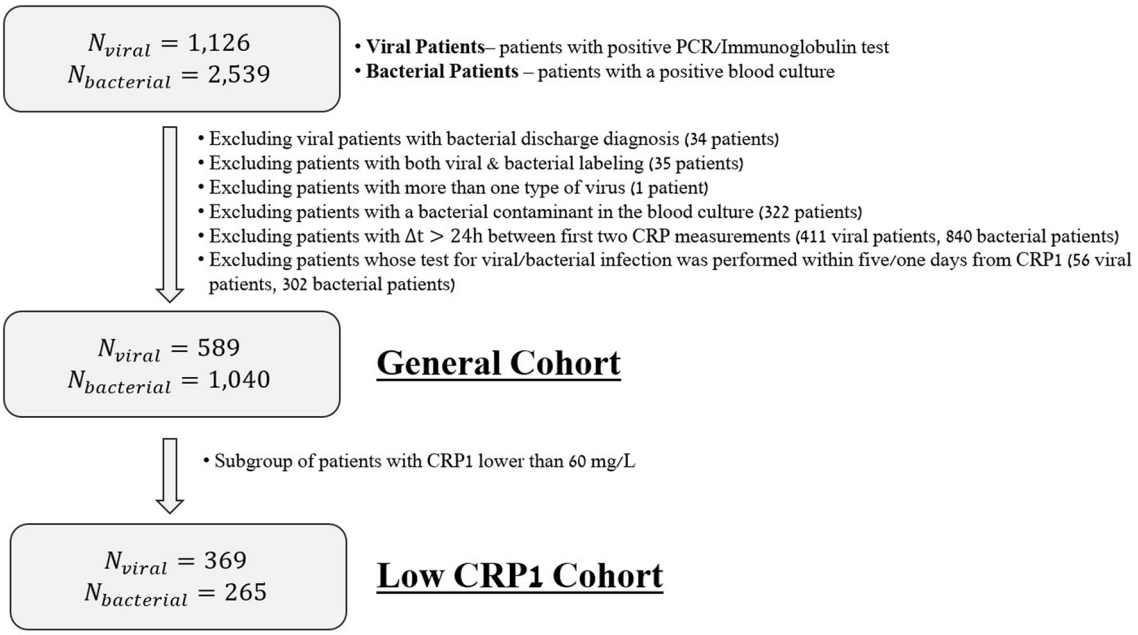

Fig. 1 Study design

Computational methods

We defined the absolute trend ('AbsTrend') as the absolute value of the difference between the first CRP measurement (CRP1) and the second (CRP2), divided by the time difference between the tests in hours (Δt):

$$\text{AbsTrend} = \frac{|\text{CRP2} - \text{CRP1}|}{\text{Time(CRP2)} - \text{Time(CRP1)}}.$$

Statistical analysis

To compare the distributions of different features on the bacterial and the viral groups, we used the non-parametric test of Mann–Whitney (MW). In order to compare the gender categorical feature we used the Pearson's Chi-squared test (Chi^2). To test the performance of a numerical parameter (e.g., CRP1, AbsTrend, etc.) as a biomarker for classification, we used receiver operator characteristic curve (ROC) analysis and calculated the area under the curve (AUC), where the positive class was bacterial infection. Standard non-parametric bootstrapping of 100 samples was used to generate the 95% confidence intervals. The mortality rates were calculated based on the proportion of patients who died within 7 or 30 days after the CRP1 measurement. To compute readmission rate, we counted patients who were admitted to the hospital within 30 days after their current admission. The readmission data were available only on 80% of the bacterial patients so in this case the relative rate was calculated.

The statistical analysis was performed using the Python programming language version 3.5.2 and the packages SciPy, NumPy and scikit-learn.

Results

Description of the study population

Six hundred and thirty-four patients were included in the low-CRP1 cohort, for whom the characteristics are presented in Table 1. Bacterial patients were older than viral patients and had similar percent of females. Viral patients have a slightly higher time difference between the two consecutive CRP measurements (Δt). The mortality rates among of the bacterial patients were higher both within 7 days and within 30 days after the CRP1 measurement. In addition, their readmission rate was higher as well.

Specific viral and bacterial types are reported in Supplementary Tables S1 and S2. Count tables of the discharge diagnosis of the patients are provided in Supplementary Tables S3 and S4.

We first evaluated the distribution of CRP1, CRP2, and AbsTrend on the low-CRP1 cohort ($n = 634$). Patients with bacterial infection presented with higher CRP concentrations on the second measurement of CRP compared to patients with viral infection (Table 1). The mean and standard deviation of AbsTrend were greater in patients with

Table 1 Demographic characteristics of the bacterial and viral groups in the low-CRP1 cohort

	Viral $N=369$	Bacterial $N=265$	AUC	MW p value	Chi^2 p value
Age, years	63.3 ± 22.7	75 ± 16.5	0.67	< 0.0001	–
Gender (% female)	174 (47.2)	132 (49.8)	0.51	–	0.62
Δ*t*, h	14.7 ± 6	13.5 ± 6.3	0.57	0.024	–
CRP1, mg/L	26.88 ± 16.97	23.03 ± 16.9	0.56	0.003	–
CRP2, mg/L	35.66 ± 35.73	75.76 ± 46.24	0.77	< 0.0001	–
AbsTrend, mg/L/h	1.04 ± 1.7	4.34 ± 10.88	0.83	< 0.0001	–
7 days mortality, *n* (%)	4 (3.5)	24 (9.1)	–	–	< 0.0001
30 days mortality, *n* (%)	16 (4.3)	45 (17)	–	–	< 0.0001
30 days readmission, *n* (%)	36 (9.8)	48/212 (22.6)	–	–	< 0.0001

Values are mean ± SD, % for women

MW p value of the Mann–Whitney test, *Chi*^{2} *p* value for the Pearson's Chi-squared test, *CRP1, CRP2* the first and second CRP measurement upon admission. In the AUC computation, the positive class was bacterial infection

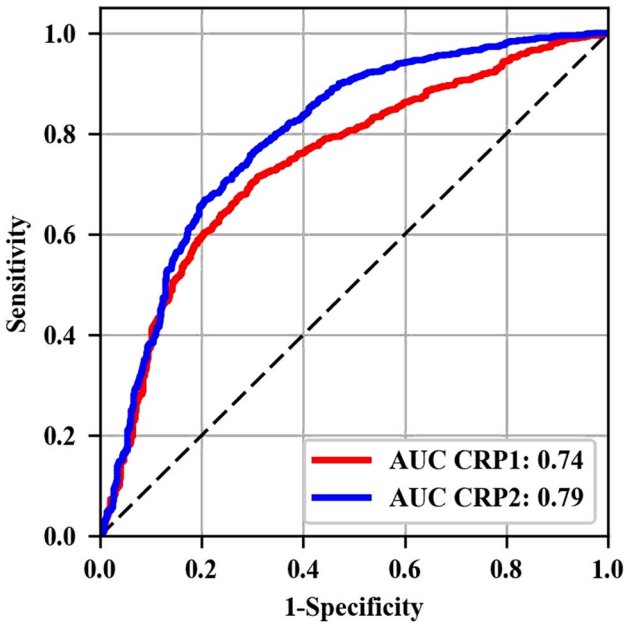

Fig. 2 Performance of CRP1 and CRP2 on the general cohort. ROC curve of the first and second CRP measurements (CRP1, CRP2) on the general cohort ($n=1629$)

bacterial infection compared to patients with viral infection (4.34 ± 10.9 and 1 ± 1.7, respectively). Δ*t* was similar in the two groups (14.7 ± 6 h and 13.5 ± 6.3 h, for bacterial and viral groups, respectively). The same analysis for the general cohort is presented in Supplementary Table S5.

We then tested CRP1 and CRP2 as biomarkers for classification into viral and bacterial types of infection. On the general cohort ($n=1629$) CRP2 had higher AUC (0.79, CI 0.77–0.81) than CRP1 (0.74, CI 0.72–0.77) (Fig. 2).

We then evaluated the classification quality of CRP1, CRP2 and AbsTrend on the 'low CRP1' group (CRP1 < 60 mg/L, $n=634$). This group was the focus of our study, since the uncertainty regarding the type of infection is the highest in it. AbsTrend was significantly better [AUC 0.83 (CI 0.8–0.86) vs. 0.57 (CI 0.53–0.6 (for CRP1 and 0.77 (CI 0.74–0.8) for CRP2]. AbsTrend above 3.47 mg/L/h discriminated patients with bacterial infection from patients with viral infection with specificity of 93.8% and sensitivity of 50.2%, enabling the detection of half of the patients with bacterial infection in the low-CRP1 group with < 7% false positive calls (Fig. 3; see Table 2 for sensitivity and specificity values for other AbsTrend cutoffs). Since increased levels of CRP are associated with cardiovascular diseases [28], age may be a confounder of our results, as our cohort is an elderly population (age 74.8 ± 16.2 and 64.7 ± 21.8 years in the bacterial and viral group, respectively) which is characterized with high prevalence of those diseases. As our EMR data did not contain information on history of cardiovascular disease, we addressed this potential bias by repeating the analysis on the sub-group of patients under age 50, who are less likely to suffer from a cardiovascular disease. For this group we got similar results [AbsTrend AUC 0.82 (CI 0.75–0.89), CRP1 AUC 0.64 (CI 0.55–0.74) and CRP2 AUC 0.77 (CI 0.68–0.87)].

In addition, in order to measure the effect of the infection severity, we compared between two sub-groups of bacterial patients in the low-CRP1 cohort: (1) bacterial patients who died less than 7 days since the time of their CRP1 measurement, and thus could be expected to be more severe cases ($n=24$), and (2) all the other bacterial patients ($n=241$). None of the data characteristics (age, gender, Δ*t*) differed significantly between the groups. Moreover, the clinical parameters were not significantly different as well—CRP1 (27.9 ± 18.2 vs. 26.8 ± 16.8, *p* value = 0.79), CRP2 (65.6 ± 51.1 vs. 76.7 ± 45.2, *p* value = 0.19), AbsTrend (3.63 ± 3.64 vs. 4.41 ± 11.35, *p* value = 0.4).

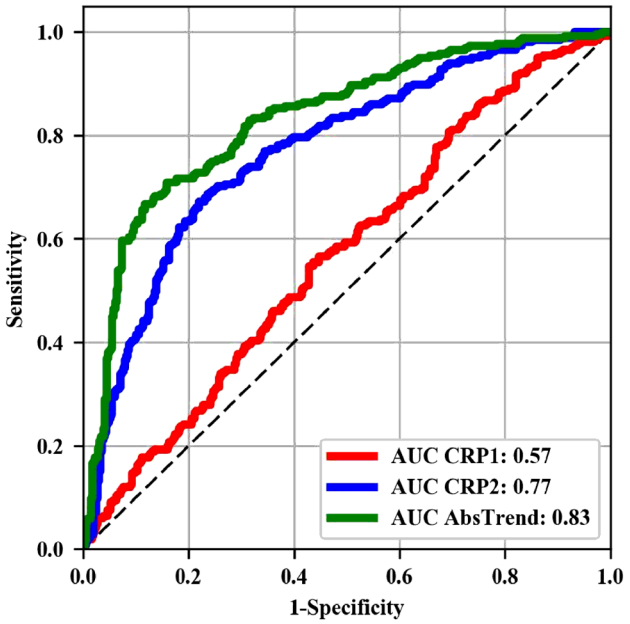

Fig. 3 Performance of CRP1, CRP2 and AbsTrend on the low-CRP1 group. ROC curve of the first and second CRP measurements (CRP1, CRP2) and AbsTrend (the absolute difference between CRP2 and CRP1 measurements divided by Δt, the time between them) on the low-CRP1 group (CRP1 < 60 mg/L, $n = 634$)

Table 2 Selected sensitivity and specificity values of the AbsTrend on the low-CRP1 group (CRP1 < 60 mg/L, $n = 634$) and the relevant positive predictive value (PPV), negative predictive value (NPV) and Youden's index

AbsTrend (mg/L/h)	Sensitivity (TPR %)	Specificity (1-FPR %)	PPV	NPV	Youden's index
7.27	9.8	98.6	83.8	60.4	0.08
5.96	21.1	97.0	83.1	62.9	0.18
5.08	29.1	95.9	83.7	65.3	0.25
4.36	38.9	94.9	84.3	68.2	0.34
3.47	50.2	93.8	85.2	72.2	0.44
2.86	60.4	91.3	83.3	76.2	0.52
2.05	70.9	84.3	76.3	79.9	0.55
1.56	72.8	78.6	71.0	80.1	0.51

A comparison of the AbsTrend distributions for the two groups (Fig. 4a) reveals a faster rise in CRP levels for patients with bacterial infection. The time difference between the measurements was roughly equal ($\Delta t = 14.7 \pm 6$ h and 13.5 ± 6.3 h for the viral and bacterial groups, respectively). The same analysis of the general cohort is presented in Supplementary S6.

To test the efficiency of AbsTrend classification in patients with low levels of CRP1, we repeated the analysis on subgroups defined by different CRP1 cutoffs (patients with CRP1 less than 10 mg/L, 20 mg/L, 30 mg/L, etc.). For all cutoffs ≤ 100 the AUC was above 0.8, and for patients with CRP1 < 30 mg/L AUC was 0.86 (Supplementary S7). This analysis confirms that AbsTrend is relevant for patients with a wide range of lower values of CRP1.

We next evaluated the impact of the time difference between CRP1 and CRP2 on the classification quality in order to search for earliest time point to assess the kinetics of CRP, by reanalyzing the subgroups of patients with $\Delta t \leq X$ hours for different values of X. Even for $\Delta t \leq 4h$, the superiority of AbsTrend was apparent, and performance improved until $\Delta t = 12h$ (Fig. 4b).

Discussion

Our study demonstrates the potential use of inflammatory host response as an internal biomarker for differential diagnosis between viral and bacterial infection. We showed that a second measurement of CRP adds valuable information regarding the etiology of the disease. Furthermore, the trend between the first two measurements of CRP (named AbsTrend) among patients with low levels of CRP upon admission, indicating the development rate of acute response over time, provided better differential diagnosis, with higher AbsTrend being indicative for bacterial etiology. This was true even if the second CRP measurement (CRP2) is taken as early as 4 h after the first (CRP1). Moreover, Fig. 4b shows that the measurement of CRP2 should be taken 12 h after CRP1 in order to get the best performance. It is worth mentioning that in our medical center CRP measurements are part of the routine blood tests, and therefore the second measurement does not indicate a more severe presentation.

Using the dynamics of a biomarker to evaluate disease risk has been suggested before; for example, the trend of hemoglobin was used to detect patients at risk for colorectal cancer [29]. For inflammation, Paran et al. suggested the kinetics of the inflammatory response following acute event, expressed as 'CRP velocity' to improve differentiation between febrile bacterial and non-bacterial illness, and showed that high 'CRP velocity' was correlated with bacterial febrile disease [30]. However, that study had a few participants, required manual review of individual charts and was based on the subjective response from the patients about the time of their symptoms' initialization.

Biomarkers that reflect the host response may offer a good solution for the insufficient discriminative power of clinical parameters measured upon ED admission and for the limitations of the currently available microbiological tests. Previous studies reported higher concentrations of CRP, procalcitonin (PCT) and interleukin-6 (IL-6) in bacterial lower respiratory tract infections compared to viral infections [31–34]. While high concentrations indicate bacterial involvement, there is still significant overlap in the lower

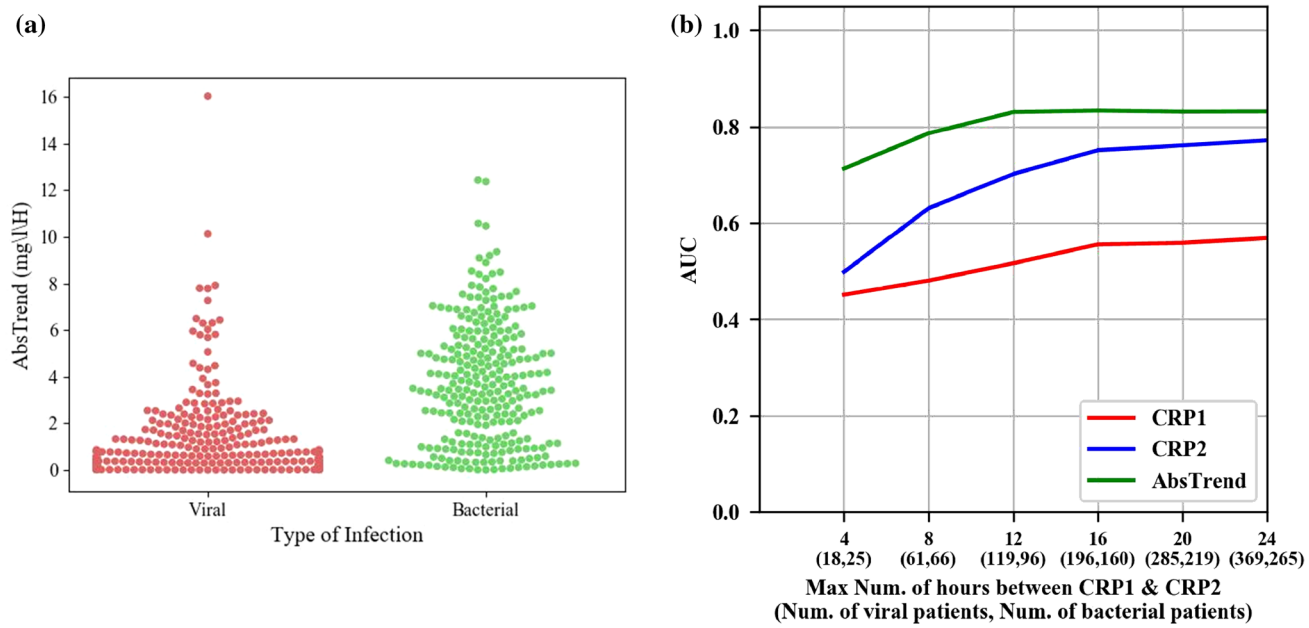

Fig. 4 CRP dynamics and AbsTrend performance for different Δt, values. **a** The distribution of AbsTrend (the absolute difference between CRP2 and CRP1 measurements divided by Δt, the time between them) values for patients with bacterial and viral infection in the low-CRP1 group (CRP1 < 60 mg/L, $n = 634$). **b** AUC of CRP1, CRP2 (the first and second CRP measurements) and AbsTrend as a function of the maximum time difference between the first two CRP measurements in the low-CRP1 group. For each x value the results are for the subgroup of patients with at most x hours between CRP1 and CRP2

range of PCT, IL-6 and CRP levels between bacterial and viral infections, which does not allow distinction between them [7]. Analysis of AbsTrend in patients admitted to the hospital with relatively low levels of CRP is beneficial in this group of uncertain etiology. We assume that those patients are at the clinical initiation of their infection course, hence using AbsTrend as an indicator could contribute to early discrimination between the groups. A second measurement of CRP within as early as 4–12 h from the first one could not only improve diagnostic prospects but also avoid early discharge of patients with bacterial infection who are in need of antibiotic treatment and hospital care. Further analysis of the kinetics of IL-6, PCT and other inflammatory biomarkers could improve the differential diagnosis and is therefore a promising area for future research. However, as our study was retrospective, and sequential measurements of those biomarkers are not routinely being drawn, they were not available in our cohort. Moreover, our comparison between the characteristics of the more severe bacterial patients and the rest suggests that the cause for the difference in AbsTrend is not based primarily on the severity of infection, but perhaps is due to the different immune system response to bacterial and viral infections.

To the best of our knowledge, there is no consensus regarding CRP cutoff for probable bacterial infection (a CRP concentration above which diagnosis of bacterial infection can be made). Previous studies [8–14] suggested at least five different cutoffs from 10 to 100 mg/L. We decided to use 60 mg/L because that value was suggested twice in the literature [10, 11] as a cutoff, and also based on our clinical experience. In fact, as we have shown in Supplementary S7, AbsTrend was a better predictor than CRP1 and CRP2 for all the suggested cutoffs.

Although our study was retrospective and our study design might elaborate post hoc exclusion scheme, to the best of our knowledge it presents the largest cohort that has been examined and analyzed in an attempt to discriminate between viral and bacterial infections based on CRP concentrations. Furthermore, our labeling method remains conservative and the same as in most of prospective studies. Having said that, further prospective studies will be needed to confirm our results and to test the relevance of AbsTrend even in time intervals shorter than 4 h.

A major advantage of our approach is that it leads to a significant improvement of differential diagnosis with little or no additional cost to the hospital, by using analytics of the available data.

Our study has several limitations; first, our inclusion criteria allowed patients with chronic diseases, which can directly affect the CRP levels (such as HIV, active malignancy, congenital immune deficiency, etc.). However, there is little reason to assume that chronically elevated CRP levels will further increase quickly enough to suggest bacterial infection, if one is not already present. In addition,

information with regard to the type of medication intake and its time of registration was not available in our EMR. Using such information may improve the differential diagnosis even further.

Another limitation is that the labeling of our cohort was based purely on the lab results. It included only patients whose samples were sent for further tests (such as PCR, immunoglobulin or blood culture). The performance of these tests suggests that the ED staff already suspected a viral or bacterial infection, so the sample population may be biased.

Our general cohort was imbalanced (roughly 2/3 bacterial and 1/3 viral), which might affect the performance of our classifier. This issue did not arise in the analysis of the low-CRP1 group, which was roughly balanced.

Our data did not include full sepsis criteria, so we could not use these criteria to compare the patients with viral and bacterial infection.

Our cohort did not represent all possible bacteria and viruses, as it was based on the population admitted to the ED: most of the patients with viral infection had influenza or respiratory syncytial virus (RSV), and the patients with bacterial infection had only bacteremia. In addition, co-infection of viral and bacterial infections is relatively common in pneumonia and we excluded co-infected patients in our cohort. Moreover, we excluded patients who had a positive viral test and a discharge diagnosis of pneumonia, since it represents a potentially bacterial infection. Hence, the diagnosis of pneumonia cases by the model might be biased. Generally, the strict exclusion criteria were aimed to create two separate groups of viral and bacterial patients, with clear microbiological confirmation and with minimal possible mislabeling of patients. Still, the utility of AbsTrend was demonstrated on the patients with RSV and influenza, who often receive unnecessary antibiotic treatment. The relevance of our results to other viral infections should be examined in further studies. Moreover, the fact that our bacterial cohort included only patients with a positive blood culture could bias the results, since it represents patients with a systemic infection and hence could be considered as a more severe infection than a viral infection. Still, we studied patients whose first CRP measurement was relatively low (< 60 mg/L) who assumingly had less severe presentation at the ED. Further research should evaluate the efficiency of the AbsTrend between groups of viral sepsis and bacterial infection.

The last limitation is the unknown pathological course of the disease, namely the time of disease onset, which precedes hospitalization time. Knowing the time difference from the disease onset (t_0) to the first or second measurement of CRP can affect the diagnosis. Presumably, using AbsTrend together with t_0 may improve the results. However, this information is subjective in nature and could not be assessed easily via retrospective EMR data analysis.

Conclusions

We conclude that using a second measurement of CRP could aid in differential diagnosis of bacterial from a viral infection at relatively low cost and in a short time frame. Our findings call for further investigation of the kinetics of acute host response and must await validation in future prospective studies.

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Author contributions DC—planned and conducted the study, collected and interpreted data, drafted the manuscript and approved the final submission. AW—collected and interpreted data, drafted the manuscript and approved the final submission. EF—collected and interpreted data, drafted the manuscript and approved the final submission. OR—planned and conducted the study, drafted the manuscript and approved the final submission. DZ—collected data and approved the final submission. IS—collected data and approved the final submission. DB—collected and interpreted data, drafted the manuscript and approved the final submission. AM—collected data and approved the final submission. ER—collected data and approved the final submission. PH—collected data and approved the final submission. SB—planned the study, interpreted data and approved the final submission. SS-T—planned the study, interpreted data, drafted the manuscript and approved the final submission. RS—planned and supervised the study, interpreted data, drafted the manuscript and approved the final submission.

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Compliance with ethical standards

Conflict of interest The authors have declared that no competing interests exist.

Ethics approval The study was reviewed and approved by Sourasky Tel Aviv Medical Center Institutional Review Board (number 0491-17).

Consent for publication The work described has not been published before and it is not under consideration for publication anywhere else. This publication has been approved by all co-authors.

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