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A second C-reactive protein (CRP) test to detect inflammatory burst in patients with acute bacterial infections presenting with a first relatively low CRP

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Abstract

A first C-reactive protein (CRP) test, as often performed by clinicians during the presentation of patients with an acute bacterial infection, might be misleading. The aim of our study was to explore the dynamic between a second CRP test taken within 12 hours from admission CRP test in a cohort of patients diagnosed with acute bacterial infection in comparison to CRP in a control group of apparently healthy individuals.

This was a historical cohort study comprised of all patients admitted to the Sourasky Tel-Aviv Medical Center, Israel, between July 2007 and March 2016. The study cohort included adult patients who were diagnosed as having an infection, assumed to be of bacterial etiology (cellulitis and erysipelas, pneumonia, cholecystitis, pyelonephritis, or septicemia), who had a CRP test during the first 6 hours of hospital admission (baseline CRP), and a successive CRP test up to 12 hours from the first one (recurrent CRP). The control group was of healthy subjects who attended our medical center for a routine annual check-up.

The study included 950 patients. Baseline CRP ranged from 0.04 to 454 mg/L. The median CRP velocity was 0.53 mg/L/h. Patients were grouped by baseline CRP into 4 groups (CRP < 10, 10–74.9, 75–199.9, ≥200). There was an increase in median CRP velocity between the first (0.48 mg/L/h) and the second (0.93 mg/L/h) groups, which then was decreased in the next 2 groups (0.46 and −2.58 mg/L/h, respectively). In 45 of 103 (44%) patients of the group of baseline CRP concentration less than 10 mg/dL with bacterial diagnosis, there was a complete overlap with CRP values of apparently healthy individuals during their routine annual checkup.

A first single low CRP result cannot exclude the presence of a significant bacterial infection. Patients with acute bacterial infection might present with a relatively low CRP value that at times correspond to normal limit CRP concentrations. A second test, obtained within 12 hours of admission, might serve as an important tool to identify patient with an evolving inflammatory burst commonly seen during acute bacterial infection.

Abbreviations: CRP = C-reactive protein, EMR- electronic medical record, IQR = interquartile range, TAMCIS = Tel Aviv Medical Center Inflammation Survey, WBC = white blood cells, wrCRP = wide range C-reactive protein.

Keywords: C-reactive protein, CRP velocity, inflammatory burst

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GI and DS contributed equally to this study.

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1. Introduction

The relation between C-reactive protein (CRP) and inflammation has been reviewed in the past.[1–3] CRP is an established inflammatory biomarker, mainly classed as an acute marker of inflammation and is the principal downstream mediator of the acute-phase response. CRP is synthesized by IL-6 dependent hepatic biosynthesis. CRP's main role in inflammation is activation of the C1q molecule in the complement pathway leading to opsonization of pathogens. CRP is commonly used by clinicians in acute bacterial diseases for both the detection of the inflammatory process and for quantization of its intensity.[4] In fact, acute bacterial infections have been repeatedly associated with increased CRP concentrations and this parameter is generally used by clinicians to clarify whether a certain patient presents a significant inflammatory response or not.[5–7] However, it is well-known that the inflammatory response to the bacterial infection is a dynamic one and a single test, as often performed by clinicians upon presentation of the patient, might not convey this dynamic information. Thus, impression that certain patients have an attenuated inflammatory response might be obtained. Moreover, such an impression might have clinical consequences expressly, in cases where clinicians decide upon discharging the patient rather than admitting the former, in the presence of relatively low CRP concentrations.[8,9]

Due to the points of potential clinical relevance, we have presently analyzed not only the admission CRP but the following CRP as well. Furthermore, we draw attention to our finding that in the presence of an inflammatory burst, a second CRP might change the clinician's impression regarding the intensity of the disease therefore, possibly changing his clinical decision as to whether a certain patient can indeed be discharged or whether he should be admitted for a closer observation. To the best of our knowledge, as opposed to what is commonly used in patients with chest pain in which case a second troponin is customarily taken, a second look at the second CRP is seldom performed in the Emergency Medicine department. On the basis of the findings of the present study, we encourage reflecting on the eventual usefulness of taking a second CRP test in cases where patients with acute bacterial infections present with relatively low CRP concentrations.

2. Methods

2.1. Study design and setting

A historical cohort study comprised of all patients admitted to the Sourasky Tel-Aviv Medical Center, Israel, a 1050 beds tertiary university affiliated hospital, serving an urban population of approximately 500,000 people, between July 2007 and March 2016. The study was reviewed and approved by the Institutional Review Board (number 0491–17).

2.2. Participants

2.2.1. Patient population. The study included patients 18 years and older who were diagnosed as having an infection, assumed to be of bacterial etiology (cellulitis and erysipelas, pneumonia, cholecystitis, pyelonephritis, or septicemia), who had a CRP test during the first 6 hours of hospital admission (baseline CRP), and a successive CRP test up to 12 hours from the first one (recurrent CRP). Patients with recurrent tests of less than 30 minutes or patients with solid or hematologic malignancy or patients with chronic inflammatory disease (including systemic lupus erythematosus, Rheumatoid arthritis, Inflammatory bowel disease, etc) were excluded from the study, as they may cause elevation of CRP values without inflammation.

2.2.2. Control group population. We have analyzed data that were collected between January 2008 and April 2016 from the Tel-Aviv Medical Center Inflammation Survey, a registered data bank of the Israeli Ministry of Justice.[10–12] This is a large cohort of subjects who attended our medical center for a routine annual check-up, and gave their written informed consent for participation (n = 19,253). This cohort was extensively investigated and reported in a series of publications in the past.[10,13–17] These apparently healthy individuals were instructed not to undergo this year's annual check-up in case of acute illness. Furthermore, each individual filled out a health check-up form before the medical tests where they were specifically asked whether they are currently suffering from any inflammatory condition. Any individual who indicated such a process was excluded from the cohort.

The study was approved by the local Ethics committee (number 02–049). The cutoff point of CRP value of 10 mg/L is an arbitrary one, which was recently suggested as a cutoff to differentiate between significant and less significant inflammation.[18] Hence, in this specific cohort, we excluded individuals with a CRP concentration of >10 mg/L; therefore, the total number of controls for comparison of CRP distribution is 18,494 participants.

2.2.3. Variables, data source, and measurement. Infectious diagnosis, of presumed bacterial etiology, was determined using ICD-9-CM codes (681, 682 for Cellulitis; 481, 482 for Pneumonia; 574, 575 for Cholecystitis; 590 for Pyelonephritis; 035 for Erysipelas; 038, 995.91, 995.92 for Septicemia) as recorded in the patient electronic medical record (EMR). Wide-range CRP (wrCRP)[19–22] was measured by ADIVIA 2400 Siemens Healthcare Diagnostics Inc., Tarrytown, NY, using latex-enhanced immunoturbidimetric method. It is based on the principle that the analyte concentration is a function of the intensity of scattered light caused by the latex aggregates. The latex particles coated with anti-CRP rapidly agglutinate in the presence of CRP-forming aggregates. This method measures the wrCRP concentration ranging 0.03 (156–164) mg/L. When the measured concentrations excide 160 mg/L, a dilution of 1:4 is performed.

Age, gender, and major comorbidities were extracted from the EMR. CRP difference was calculated as recurrent CRP minus baseline CRP. CRP velocity was calculated as CRP difference divided by the hours between the 2 tests. CRP ratio was calculated as recurrent CRP divided by baseline CRP.

2.2.4. Statistical methods. Categorical variables were reported as numbers and percentages, and continuous variables were reported as medians with interquartile range (IQR). Continuous variables were compared between groups using Kruskal–Wallis test or Mann–Whitney test. Correlation between continuous variables was evaluated by the Spearman rank correlation coefficient.

Baseline CRP was compared between infectious diagnoses after exclusion of patients with concurrent infectious diagnosis. Chi-squared Automatic Interaction Detection (CHAID) analysis was used to identify the optimal threshold values of baseline CRP that divided the CRP ratio and CRP velocity into most homogenous groups. The threshold values were rounded for

Table 1

Patients' characteristics.

	All cohort (n = 950)
Male, n (%)	497 (52.3%)
Age, yr, median (IQR)	70 (47–84)
Infectious diagnosis, n (%)	
Cellulitis	419 (44.1%)
Septicemia	284 (29.9%)
Pneumonia	138 (14.5%)
Pyelonephritis	106 (11.2%)
Erysipelas	25 (2.6%)
Cholecystitis	14 (1.5%)
Comorbidity, n (%)	
Diabetes mellitus	255 (26.8%)
Hyperlipidemia	218 (22.9%)
Hypertension	148 (15.6%)
Congestive heart failure	93 (9.8%)
Ischemic heart disease	163 (17.2%)
Myocardial infarction	20 (2.1%)
Chronic renal failure	92 (9.7%)
Obesity	74 (7.8%)

IQR = interquartile range.

ease. A 2-tailed P value less than .05 was considered as statistically significant. All statistical analyses were performed with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

3. Results

The study included 950 patients, 497 of them were male (52.3%). The median age was 70 years (IQR 47–84). Patients' characteristics are presented in Table 1. Ninety-seven percent of the patients had a baseline CRP test in 3 hours from admission (median 1.2 hours, IQR 0.8–1.6). Thirty-three patients had more than one infectious diagnosis. Cellulitis was the most common diagnosis (419 patients). The baseline CRP ranged from 0.04 to 454 mg/L. Patients with cellulitis had lower baseline CRP (median 50.2 md/L, IQR 18.8–133.2) than patients with pneumonia (median 104.4 md/L, IQR 36.2–165.4, $P < .001$), septicemia (median 94.7 md/L, IQR 33.9–158.9, $P < .001$), and pyelonephritis (median 118.4 md/L, IQR 38.8–174.9, $P < .001$).

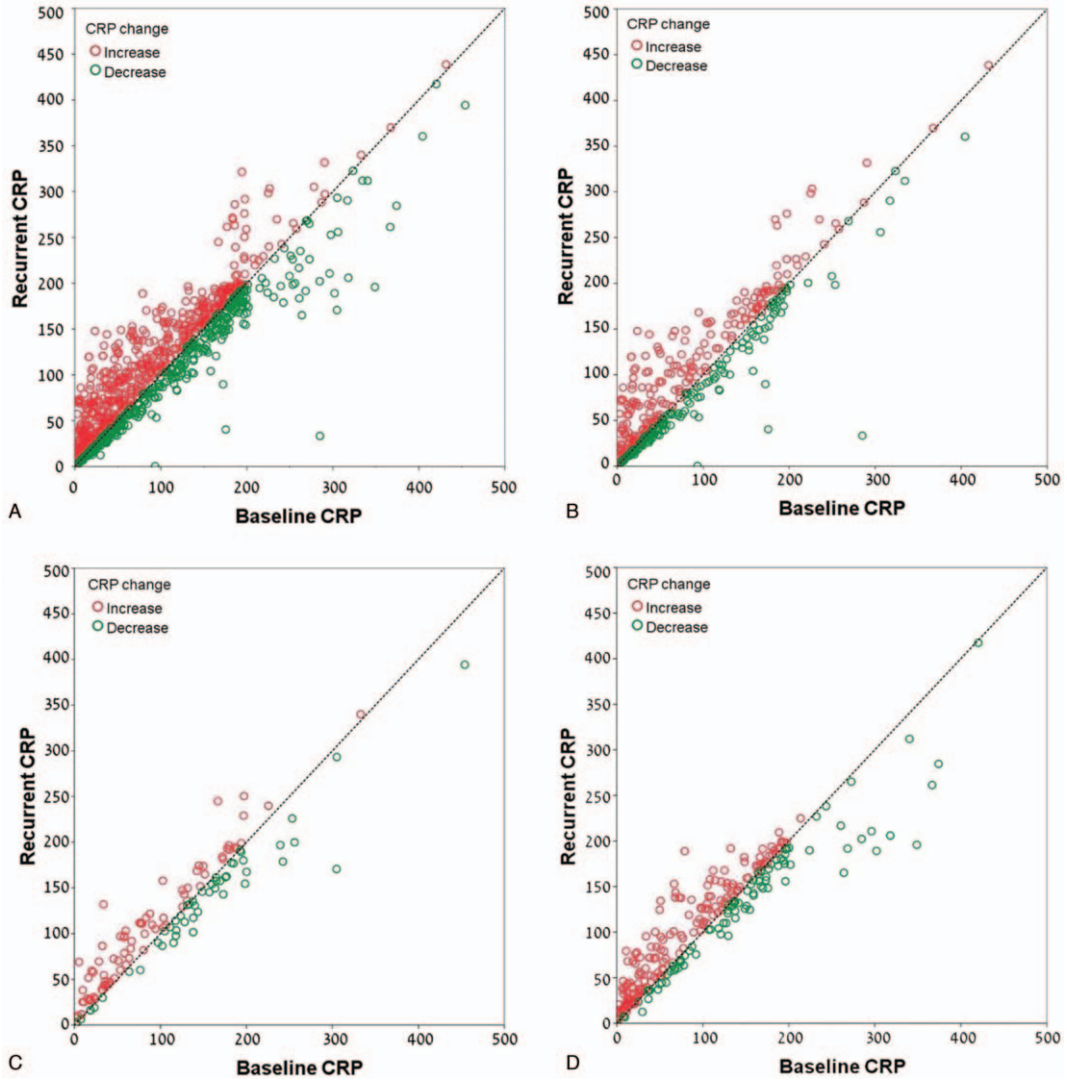

Figure 1. Correlation between baseline C-reactive protein and recurrent C-reactive protein. Red cycles express patients with recurrent C-Reactive Protein higher than baseline and green cycles represent patients with recurrent C-reactive protein lower than baseline. (A) All cohort, (B) Cellulitis, (C) Pneumonia, (D) Septicemia. CRP = C-reactive protein.

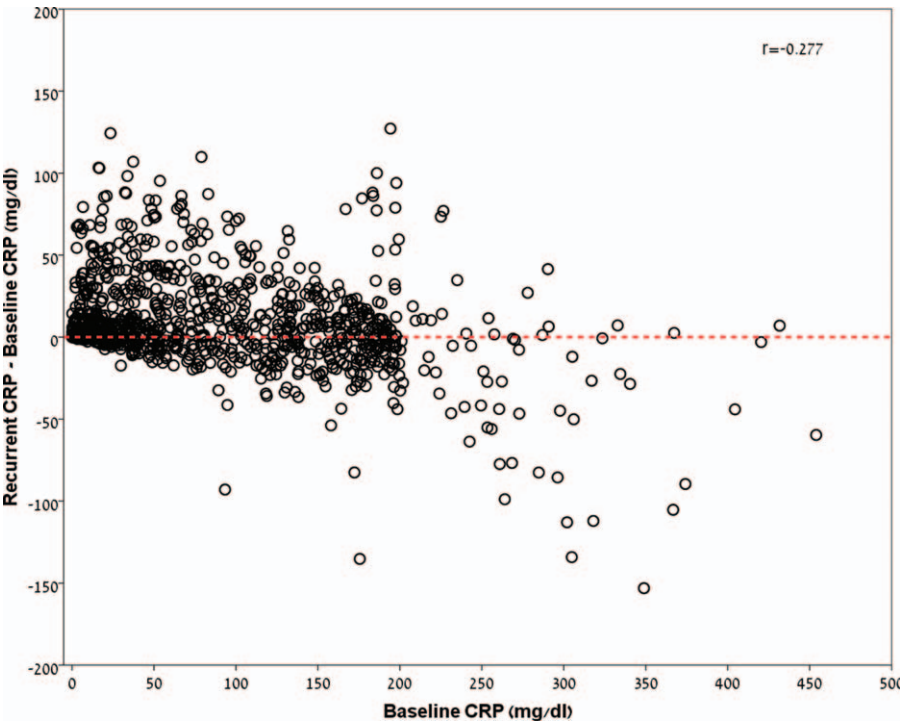

Figure 2. The association between baseline C-reactive protein and C-reactive protein difference. CRP = C-reactive protein.

There was no statistical difference in baseline CRP between other infectious diagnoses. Correlation between baseline CRP and recurrent CRP is presented in Figure 1A and the association between CRP difference and baseline CRP is presented in Figure 2.

The median CRP velocity was 0.53 mg/L/h. When patients were grouped by baseline CRP according to their initial CRP using CHAID, we revealed 4 groups (CRP < 10, 10–74.9, 75–199.9, ≥200). There was an increase in median CRP velocity between the first (0.48 mg/L/h) and the second (0.93 md/L/h)

Table 2

Baseline C-reactive protein, recurrent C-reactive protein, C-reactive protein difference, C-reactive protein velocity, and C-reactive protein ratio in all cohorts and in subgroups of patients according to their baseline C-Reactive Protein as revealed by CHAID analysis (A) and (B) and according to their baseline C-Reactive Protein ranking (x100 lowest, 100 highest C-reactive protein values, C).

	n	Baseline CRP, mg/L	Recurrent CRP, mg/L	CRP difference, mg/L	CRP velocity, mg/L/h	CRP ratio	Time between baseline and recurrent CRP, hr
All cohort							
CRP	950	75.4 (26.7–153.4)	96.5 (39.3–157.9)	4.6 (–4.5 to 21.9)	0.53 (–0.52 to 2.78)	1.06 (0.93–1.42)	9.2 (6.8–10.8)
Grouping by baseline CRP (A)							
<10	103	5.1 (2.2–7.3)	10.2 (4.7–20.7)	3.3 (0.0–15.0	0.48 (0.00–2.31)	1.99 (1.0–5.44)	8.7 (7.5–10.3)
10–74.9	372	35.0 (20.6–51.6)	47.7 (29.5–72.0)	7.6 (–1.0 to 35.01)	0.93 (–0.11 to 3.90)	1.24 (0.97–1.89)	9.4 (6.9–11.0)
75–199.9	411	142.5 (x108.7–175.4)	149.9 (114.4–176.6)	3.79 (–9.7 to 18.3)	0.46 (–1.25 to 2.29)	1.02 (0.93–1.14)	9.4 (6.7–10.8)
≥200	64	263.1 (231.5–305.1)	229.7 (198.3–289.8)	–22.0 (–53.9 to 2.0)	–2.58 (–6.3 to 0.27)	0.92 (0.81–1.01)	8.6 (5.9–10.7)
P		N/A	<.001	<.001	<.001	<.001	.193
Grouping by baseline CRP (B)							
<10	103	5.1 (2.2–7.3)	10.2 (4.7–20.7)	3.3 (0.0–15.0	0.48 (0.00–2.31)	1.99 (1.0–5.44)	8.7 (7.5–10.3)
10–19.9	87	15.1 (12.7–17.7)	24.9 (15.9–44.8)	8.5 (0.1–30.1)	1.00 (0.06–4.16)	1.57 (1.01–3.16)	9.4 (6.9–11.0)
20–34.9	99	26.9 (22.7–32.3)	33.9 (25.9–57.5)	6.2 (–0.1–29.0)	0.83 (–0.04 to 2.83)	1.23 (0.99–2.09)	9.3 (7.4–10.9)
35–74.9	186	51.5 (41.9–62.3)	65.2 (46.7–91.7)	7.7 (–3.1 to 38.0)	1.15 (–0.42 to 3.97)	1.16 (0.94–1.71)	9.5 (6.7–11.1)
75–99.9	76	85.9 (79.7–93.3)	97.7 (80.2–114.1)	11.4 (–7.1 to 28.9)	1.25 (–0.74 to 3.88)	1.14 (0.93–1.33)	9.4 (6.6–10.8)
100–199.9	335	156.1 (129.0–179.6)	158.0 (132.1–181.3)	2.71 (–10.6 to 15.4)	0.32 (–1.39 to 1.91)	1.02 (0.93–1.10)	9.3 (6.7–10.8)
≥200	64	263.1 (231.5–305.1)	229.7 (198.3–289.8)	–22.0 (–53.9 to 2.0)	–2.58 (–6. to –0.27)	0.92 (0.81–1.01)	8.6 (5.9–10.7)
P		N/A	<.001	<.001	<.001	<.001	.541
Grouping by baseline CRP (C)							
Lowest values	100	5.08 (2.18–7.28)	8.9 (4.5–19.3)	3.19 (v0.02–14.84)	0.47 (0.00–2.25)	1.98 (0.99–5.73)	8.7 (7.0–10.3)
Highest values	100	226.1 (197.1–283.1)	206.9 (190.8–265–4)	–6.97 (–41.34 to 4.74)	–1.15 (–4.10 to 0.56)	0.97 (0.85–1.02)	8.9 (5.8–10.7)
P		N/A	<.001	<.001	<.001	<.001	.847

CRP = C-reactive protein.

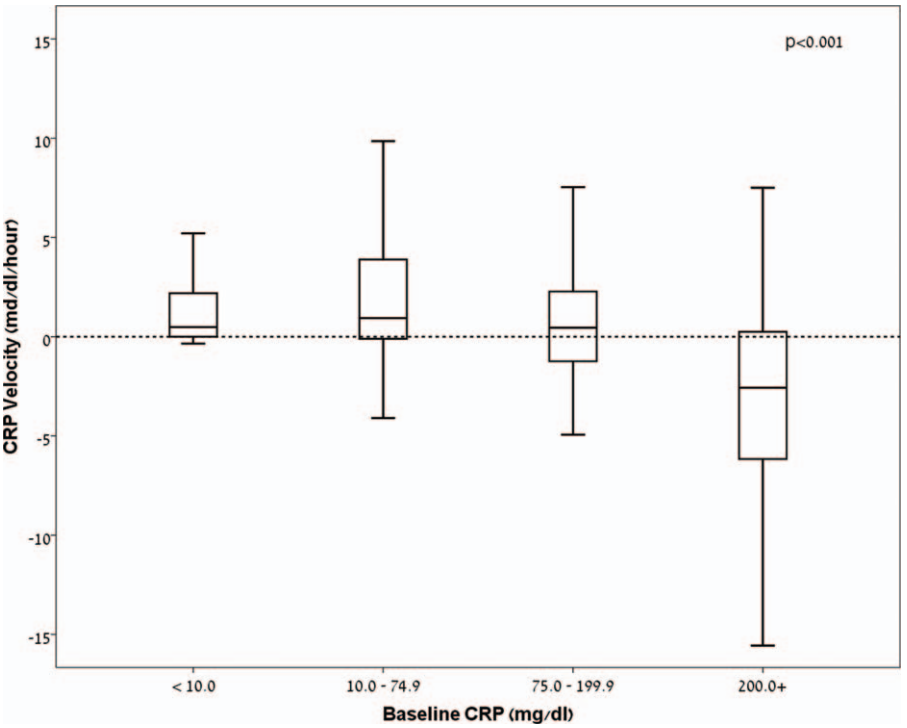

Figure 3. Box and whisker plot of C-reactive protein velocity by baseline C-reactive protein. CRP = C-reactive protein.

groups, which then was decreased in the next 2 groups (0.46 and -2.58 mg/L/h, respectively, Table 2 grouping A, Fig. 3).

The median CRP ratio was 1.06. When patients were grouped by baseline CRP according to their CRP ratio using CHAID, we revealed threshold values of approximately 10, 20, 35, 75, 100, and 200. There was a consistent decrease in median CRP ratio between groups (Table 2 grouping B, Fig. 4A).

There was no difference in CRP tests time interval between groups (Table 2A, Table 2B). There were no statistical differences in CRP velocity and CRP ratio between infectious diagnosis ($P = .265$, $P = .094$, respectively) and between females and males ($P = .310$, $P = .356$, respectively). There were weak correlations between age and CRP velocity or CRP ratio ($r = 0.096$, $r = 0.119$, respectively).

In addition, we ranked the baseline CRP and compared the 100 patients with the lowest values to the 100 patients with the highest values (Table 2C). The median CRP velocity was positive in the lowest CRP group, while it was negative in the highest CRP group ($P < .001$). The median CRP ratio in the lowest group was approximately 2 indicating the baseline CRP value during the short follow-up multiplied; however, the baseline CRP in the group with the highest CRP was 1 indicating no change ($P < .001$). Patients in the highest group had significantly higher white blood cells (WBCs) count, neutrophil count, creatinine and lower albumin, hemoglobin, and hematocrit (Table 3). There were no statistical differences in age, gender, infectious diagnosis, comorbidity, and CRP tests time interval between the 2 groups (Tables 2C and 3).

In order to evaluate if and how much the group of patients with CRP below 10 mg/L differs from normal distribution of CRP values, we compared their CRP measurements to the ones of the Tel Aviv Medical Center Inflammation Survey (TAMCIS). Namely, a long-term, ongoing cardiovascular cohort study evaluating stress and inflammation in apparently healthy working adults admitted to our medical center for routine annual medical check-ups. The CRP distributions of patients and controls with values below 10 mg/L are presented in Figure 5.

In this group of patients with acute infections of probable bacterial etiology and low (<10 mg/L) CRP concentrations, the difference from the expected value that is seen in apparently healthy individuals is small if any.

Furthermore, to evaluate the CRP changes in different infectious diseases, we analyzed patients separately with the 3 most common infectious diagnoses in our data, after removing patients with concurrent infection. Patient's characteristics are presented in Table 4. Similar pattern of association between baseline CRP and recurrent CRP was observed (Fig. 1B–D). As for the entire cohort, patients with each infectious diagnosis were grouped separately by baseline CRP according to their CRP ratio using CHAID (Table 5). Despite the fact that different baseline CRP threshold values were observed for each infectious disease, lower baseline CRP values were associated with higher CRP ratio in all infectious diagnosis.

4. Discussion

We have presently analyzed the CRP dynamic within the first 12 hours of hospitalization in a cohort of patients, with an assumed diagnosis of a bacterial infection, who were admitted to the departments of Internal Medicine and Dermatology at the Sourasky Tel-Aviv Medical Center. Our main finding is that regardless of the type of infection (cellulitis, pneumonia, septicemia, etc), individuals who present with relatively low CRP concentrations are expected to present significantly higher concentrations within a few hours, occasionally even whilst patients are evaluated and treated at the department of

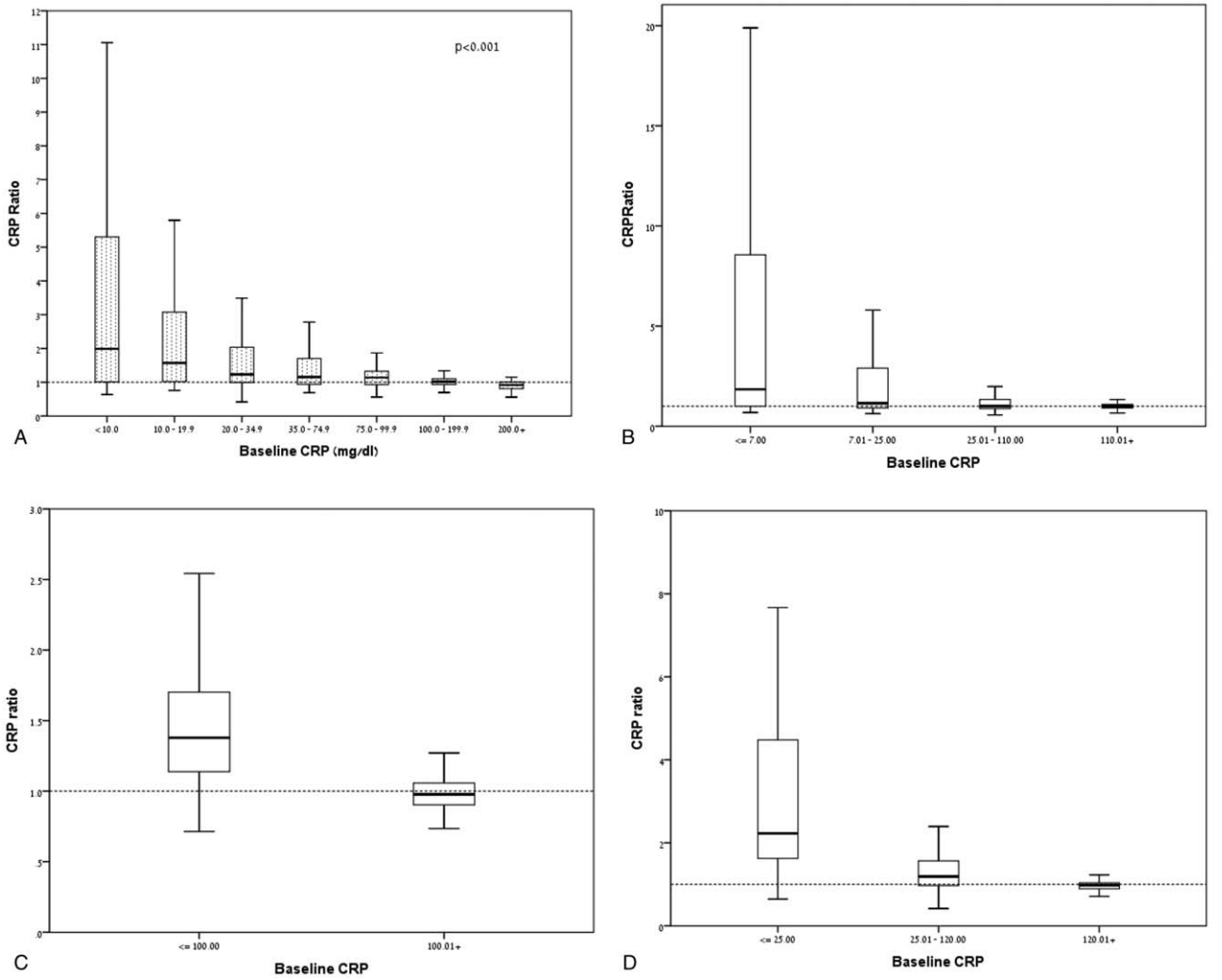

Figure 4. Box and whisker plot of C-reactive protein ratio by baseline C-Reactive Protein. (A) All cohort, (B) Cellulitis, (C) Pneumonia, (D) Septicemia. CRP = C-reactive protein.

Emergency Medicine. This phenomenon was not noted in individuals, whom at the time of admission presented high CRP concentrations.

The cohort of the present report was composed of patients who were found to be sick enough to be admitted to the hospital. We do not know if the CRP concentration was taken into consideration by the ER team regarding the decision of whether to admit the patient or not. In our view, this is one of the strengths of this study, as it is obvious that the retrospective patients with the relatively low CRP concentrations were admitted despite of their low CRP.

Thus, it is clearly visible that a first and single low CRP result cannot exclude the presence of a significant bacterial infection. In fact, within a few hours, those individuals presented a higher CRP that at times could even reach concentrations that were 5 to 10 times higher than the first one.

This dynamic change, which occurs within few hours, is the main message of the present study. Namely, that in the presence of an acute bacterial infection, a single low CRP result might not be sufficient to make solid clinical decisions. On the contrary, such a low CRP result might give an erroneous impression of a low-grade inflammatory response suggesting a nonserious infection. Paradoxically enough, it is this group that demonstrated an inflammatory burst within a short period of time.

Assuming CRP concentration below 10 mg/L to be considered in the normal range for microinflammation of apparently healthy individuals, it is clearly noticed that patients with acute infection of presumed bacterial origin can present to the ER with CRP concentrations that overlap with the CRP distribution of the control group.

We had presently used data obtained from our cohort of apparently healthy individuals, who were evaluated during their annual routine check-up in Tel-Aviv Sourasky Medical center, to clarify the magnitude of overlap between CRP values of patients who presented low admission concentrations. In 45 (44%) of a group of 103 patients with CRP concentration <10 mg/dL, we found a complete overlap with individuals who had no signs or symptoms of any infective or inflammatory disease during their routine annual checkup. Variation of repeated CRP measurements was addressed previously when considering CRP seasonality throughout the year in a group of healthy individuals, and showed lack of change in CRP values.[23] In addition, we have

Table 3

Comparison of patients that ranked as having the 100 lowest baseline C-reactive protein values to those with 100 highest baseline C-reactive protein values[*].

	100 subjects with lowest baseline CRP	100 subjects with highest baseline CRP	*P*
Male	52 (52.0%)	46 (46.0%)	.396
Age, yr	69.0 (35.8–84.0)	71.0 (48.0–81.0)	.481
Comorbidity			
Obesity	8 (8%)	6 (6%)	.579
Myocardial infarction	0 (0%)	3 (3%)	.246
Hyperlipidemia	22 (22%)	20 (20%)	.728
Ischemic heart disease	13 (13%)	18 (18%)	.329
Hypertension	17 (17%)	14 (14%)	.558
Diabetes mellitus	22 (22%)	26 (26%)	.508
Congestive heart failure	4 (4%)	8 (8%)	.234
Chronic renal failure	6 (6%)	8 (8%)	.579
Infectious diagnosis			
Cholecystitis	1 (1%)	3 (3%)	
Pneumonia	8 (8%)	17 (17%)	
Septicemia	21 (21%)	29 (29%)	
Cellulitis	56 (56%)	34 (34%)	
Pyelonephritis	8 (8%)	11 (11%)	
Erysipelas	2 (2%)	2 (2%)	
More than one	4 (4%)	4 (%)	
Time to baseline CRP test, hr	1.19 (0.84–1.60)	1.20 (0.88–1.73)	.755
Albumin, g/L	39 (35–41)	35 (31–38)	<.001
Creatinine, mg/dL	1.02 (0.90–1.33)	1.41 (1.09–2.17)	<.001
eGFR, mL/min	67 (47–86)	43 (22–75)	<.001
Hemoglobin, g/dL	13.3 (11.8–14.5)	12.2 (x10.8–13.4)	<.001
Hematocrit (%)	40.0 (36.0–42.8)	37.0 (33.0–40.0)	<.001
White blood cells, $x10^3/\mu L$	10.45 (8.18–15.10)	17.15 (12.93–23.23)	<.001
Neutrophils count, $x10^3/\mu L$	8.35 (5.33–12.48)	14.70 ($\times$10.68–19.40)	<.001
Lymphocytes count, $x10^3/\mu L$	1.60 (0.63–2.48)	1.00 (0.70–1.50)	.001
Monocytes count, $x10^3/\mu L$	0.60 (0.40–0.88)	0.80 (0.53–1.30)	.001
Eosinophils count, $\times10^3/\mu L$	0.10 (0.00–0.20)	0.00 (0.00–0.00)	<.001
Platelets, $\times10^3/\mu L$	239 (189–293)	217 (155–298)	.363

CRP = C-reactive protein, eGFR = estimated glomerular filtration rate.
[*] All continuous variables are presented as median (interquartile range).

Table 4

Characteristics of patients with the most 3 common single infections[*].

	Cellulitis (n = 401)	Pneumonia (n = 126)	Septicemia (n = 253)
Male, n (%)	245 (61.1%)	64 (50.8%)	141 (55.5%)
Age, yr	59 (40–76)	80 (62–87)	83 (69–89)
Comorbidity, n (%)			
Diabetes Mellitus	116 (28.9%)	28 (22.2%)	83 (32.7%)
Hyperlipidemia	90 (22.4%)	34 (27.0%)	64 (25.2%)
Hypertension	56 (14.0%)	26 (20.6%)	46 (18.1%)
Congestive heart failure	32 (8.0%)	10 (7.9%)	42 (16.5%)
Ischemic heart disease	62 (15.5%)	24 (19.0%)	63 (24.8%)
Myocardial infarction	2 (0.5%)	3 (2.4%)	14 (5.5%)
Chronic renal failure	26 (6.5%)	5 (4.0%)	52 (20.5%)
Obesity	44 (11.0%)	10 (7.9%)	14 (5.5%)
Albumin, g/L	38 (35–42)	38 (34–40)	32 (28–38)
Creatinine, mg/dL	1.1 (0.9–1.4)	1.1 (.9–1.5)	1.4 (1.1–2.3)
eGFR, mL/min	85.5 (53.6–108)	69 (36.3–94.3)	33.5 (18.8–57.8)
Hemoglobin, g/dL	13 (11.4–14.3)	12.4 (11.4–13.6)	11.7 (x10.1–13.2)
Hematocrit (%)	39 (34–42)	37 (34–41)	36 (31–40)
White blood cells, x103/μL	11.9 (8.9–15.9)	12.3 (8.1–17.3)	14.5 (9.8–20.1)
Neutrophils count, x103/μL	8.9 (6–13.4)	9.7 (6.2–14.5)	12.3 (8.3–17.8)
Lymphocytes count, x103/μL	1.5 (0.9–2.2)	1.2 (0.8–1.6)	0.9 (0.6–1.4)
Monocytes count, x103/μL	0.8 (0.6–1)	0.8 (0.6–1.1)	0.7 (0.4–1.2)
Eosinophils count, x103/μL	0.1 (0–0.2)	0 (0–0.1)	0 (0–0.1)
Platelets, x103/μL	236 (182–299)	237 (179–298)	253 (165–335)

eGFR = estimated glomerular filtration rate.
[*] All continuous variables are presented as median (interquartile range).

also specifically evaluated in the past repeated CRP tests in healthy patients with very low CRP values. No difference was found in these repeated tests.[9] Therefore, it seems unlikely that the changes of repeated CRP values are caused by variation of measurement unrelated to an infectious etiology.

Even in patients with low CRP values <10 mg/dL, there are number of cases showing negative CRP velocity despite the average velocity being positive (Fig. 1), meaning that decreasing

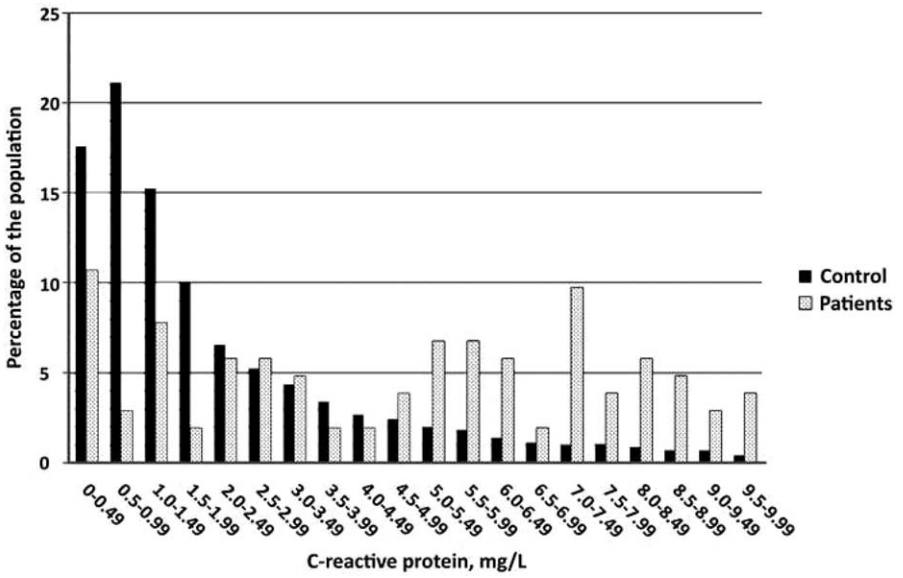

Figure 5. C-Reactive protein distributions of patients and controls with values below 10 mg/L. CRP = C-reactive protein.

Table 5

Recurrent C-reactive protein, C-reactive protein difference, C-reactive protein velocity, and C-reactive protein ratio in patients with the most 3 common single infection and in subgroups of patients in each infection diagnosis according to their baseline C-reactive protein as revealed by CHAID analysis.

		n	Baseline CRP, mg/L	Recurrent CRP, mg/L	CRP difference, mg/L	CRP velocity, mg/L/h	CRP ratio	Time between baseline and recurrent CRP, hr	Time to baseline CRP test, hr
Cellulitis	All	401	50.1 (18.7–133.1)	67.6 (28.6–142.5)	1.3 (–4.3 to 18.6)	0.1 (–0.5 to 2.5)	1.1 (0.9–1.3)	9.6 (7.8–10.9)	1.2 (0.9–1.8)
Grouping by baseline CRP	CRP ≤7	38	3.3 (1.1–5.6)	6.2 (2.0–27.3)	2.5 (0.0–23.2)	0.2 (0–3)	1.8 (1.0–8.7)	8.7 (7.8–10.6)	1.2 (0.8–1.7)
	7<CRP≤25	86	15.2 (x10.5–19.3)	17.6 (11.6–34.7)	1.7 (–1.0 to 24.7)	0.2 (–0.1 to 3.5)	1.1 (0.9–2.9)	9.5 (8.0–11.0)	1.1 (0.8–1.5)
	25<CRP≤110	158	51.4 (37.5–78.6)	57 (39.3–92.4)	0.8 (–5.9–24.5)	0.1 (–0.6–2.7)	1.0 (0.9–1.3)	9.8 (7.9–11.1)	1.2 (0.9–1.8)
	CRP>110	119	172.3 (148.4–195.3)	175.1 (143.3–198.5)	0.4 (–15.5–14.1)	0.1 (–1.4–2)	1.0 (0.9–1.1)	9.7 (7.4–10.9)	1.3 (0.9–2.0)
	P		NA	<.001	.002	.003	<.001	.558	.167
Pneumonia	All	126	104.4 (36.3–165.4)	111.2 (59.1–162)	5.5 (–5.2 to 18.5)	0.7 (–0.7 to 2.7)	1.1 (0.9–1.4)	8.6 (6.7–10.6)	1.1 (0.8–1.7)
Grouping by baseline CRP	CRP ≤100	59	34.4 (18.7–63.7)	57.9 (28.6–90.2)	11.1 (5.1–33.9)	1.7 (0.7–3.7)	1.4 (1.1–1.7)	8.3 (6.5–10.6)	1.1 (0.8–1.6)
	CRP >100	67	163.6 (131.2–192.8)	157.9 (130.6–191.2)	–3.3 (–15.4 to 11.5)	–0.4 (–1.9 to 1)	1.0 (0.9–1.1)	9.3 (6.9–10.7)	1.2 (0.7–1.7)
	P		NA	<.001	<.001	<.001	<.001	.497	.818
Septicemia	All	253	94.7 (34–158.9)	110.8 (51.3–158.2)	5.1 (–5.2–20.7)	0.7 (–0.7 to 2.5)	1.1 (1.0–1.6)	8.1 (5.6–10.5)	1.1 (0.8–1.5)
Grouping by baseline CRP	CRP ≤25	50	11.2 (5.9–18)	23.1 (13.2–39.4)	10.9 (4.6–26.3)	1.3 (0.5–3.1)	2.2 (1.6–4.6)	8.3 (6.3–10.8)	1.2 (0.7–1.6)
	25.01<CRP≤120	99	64.6 (43.3–89.5)	76.6 (54.2–114.4)	11.6 (–1.6–33.7)	1.5 (–0.1–4.5)	1.2 (1.0–1.6)	8.0 (5.6–10.7)	1.1 (0.8–1.4)
	CRP>120	105	167.4 (137.8–194.2)	167.8 (143.8–191)	–3.4 (–16.9 to 6.6)	–0.5 (–2.8 to 0.8)	1.0 (0.9–1.0)	8.1 (5.3–10.3)	1.1 (0.8–1.6)
	P		NA	<.001	<.001	<.001	<.001	.736	.775

CRP = C-reactive protein.

second CRP level in this group of patients does not rule out a serious underlying infection. This phenomenon may be related to immune paresis, which can accompany bacterial infections.

A single CRP test with significantly high concentration is of clear clinical utility when facing individuals with bacterial infections.[24] Even, though, patients who present with higher CRP values may have negative CRP velocity upon a repeated CRP measurement. This phenomenon may be caused due to consumption of CRP in tissues during hyperinflammation.[1] The present study was performed to clarify that individuals with acute infections of presumed bacterial etiology might also present with a relatively low CRP value, which at times correspond to within normal limit CRP concentrations. Moreover, a second test, obtained within a couple of hours might reveal the presence of much higher concentrations and unravel the underlying cytokine storm, completely changing the clinician's erroneous impression of a relatively mild infection/inflammation and as shown in a previous study the kinetics of CRP may even assist in the differential diagnosis between acute bacterial and viral infection.[25] Hence, we recommend a second CRP test to better evaluate the evolving inflammatory process.

There are several limitations to this present study, the main one being its retrospective nature. An additional limitation is the lack of information about the precise timing of disease onset, a timing that has an influence on the concentration of the final CRP test. Still another limitation is that we do not know if the patients with a diagnosis of pneumonia really had a purely bacterial infection. Finally, we did not consider the eventual type of bacteria involved in the infection, another factor that should have an influence on the intensity of the inflammatory response.[26]

We conclude that a single low CRP test cannot be taken as a reliable biomarker for the exclusion of a significant infective/inflammatory condition. In individuals with acute infections/inflammation of presumed bacterial infection, a secondary test that is taken within a few hours might convey additional information that might change the clinician's impression regarding the intensity of the inflammatory response. To the best of our knowledge, this is the first study that describes in details the dynamic CRP changes during the first hours of hospitalization pointing out the need for additional information before conclusions are made regarding the intensity of the inflammatory response in patients who present with acute bacterial infections and a single low concentration CRP test.

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