Observational Study

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Septic patients presenting with apparently normal C-reactive protein

A point of caution for the ER physician

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Abstract

The presentation of septic patients with low C-reactive protein (CRP) concentrations to the emergency room (ER) might convey an erroneous impression regarding the severity of the disease.

We analyzed a retrospective study of septic patients admitted to the internal medicine departments of a relatively large tertiary medical center, following admission to the ER. These patients had CRP concentrations of <31.9 mg/L, the determined cut-off for CRP concentrations in a large cohort of apparently healthy individuals in the community (n = 17,214, upper limit of mean + 3 standard deviations).

By processing the electronic medical records, we found 2724 patients with a diagnosis of sepsis, 476 of whom had an admission CRP concentration of <31.9 mg/L. Following further analysis of these records, we found that 34 of the 175 patients (19.4%) who fulfilled the definition of sepsis, died within 1 week of hospitalization. Of special interest was the finding that within <24 h, a significant increment from a median CRP of 16.1 mg/L (IQR 7.9–22.5) to 58.6 mg/L (IQR 24.2–134.4), ($P < .001$) was noted, accompanied by a velocity change from 0.4 ± 0.29 to 8.3 ± 24.2 mg/L/h following antibiotic administration ($P < .001$).

ER physicians should take into consideration that septic patients with a high in-hospital mortality rate can present with CRP concentrations that are within the range observed in apparently healthy individuals in the community. A second CRP test obtained within 24 h following antibiotic administration might influence attitudes regarding the severity of the disease.

Abbreviations: CRP = C-reactive protein, ER = emergency room, IQR = interquartile range, TAMCIS = Tel Aviv Medical Center Inflammation Survey, wr = wide range.

Keywords: C-reactive protein, immunosuppression, sepsis, velocity

1. Introduction

Physicians in the emergency room (ER) use laboratory tests including C-reactive protein (CRP) to reveal the presence of an inflammatory response and to assess its severity.[1–6] However, it is known that sepsis might be associated with some degree of immunomodulation which could result in immunosuppression,[7,8] raising the possibility that this immune paresis could result in reduced release of cytokines that are involved in the production of CRP. While most ER physicians have already recognized the possibility that patients with sepsis might present with low concentrations of this biomarker, the magnitude of overlap with CRP concentrations, as detected in apparently healthy individuals, has not yet been investigated.

We performed a comparative analysis between CRP concentrations detected in septic patients during their presentation to the ER, and those detected in a relatively large cohort of apparently healthy individuals from the community, who underwent a routine annual health-screening program. Our significant finding was that septic patients did indeed present to the ER with CRP concentrations that were completely in the range that can be seen in asymptomatic apparently healthy individuals. ER physicians should, therefore, interpret normal CRP concentrations in the context of sepsis with caution.

2. Methods

2.1. Ethics approval

The Sourasky Tel Aviv Medical Center Institutional Review Board approved the study (Numbers 0491-17 and 02-049).

2.2. Study design and setting

A historical cohort study comprised all patients admitted to the Sourasky Tel Aviv Medical Center, Israel (a 1050-bed tertiary university affiliated hospital, serving an urban population of approximately 500,000 people), between Oct 2011 and Nov 2017. The study was reviewed and approved by the Institutional Review Board (number 0491-17).

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2.3. Participants

2.3.1. Septic patients. The study included patients 18 years of age and older who were diagnosed with sepsis. Patients were included if they were hospitalized in one of our internal medical departments via our ER, with a diagnosis of sepsis coded on their admission or discharge records, and who had at least 1 CRP measurement is taken in the ER (baseline CRP).

Codes for sepsis included ICD-9 codes '995.90', '995.91', '995.92', '995.94'. All medical records were retrospectively reviewed by 2 senior physicians, one of them (AW) being a specialist in infectious diseases. The investigators confirmed the diagnosis of sepsis according to the classical definition of at least 2 systemic inflammatory response syndrome criteria and a suspected or proven infection.[9]

The initial sepsis cohort included a total of 2724 patients, whose hospital records were reviewed manually in order to confirm a sepsis diagnosis of all patients with CRP measurements below 31.9 mg/L. Thus, our study comprised 476 sepsis patients with CRP levels within the normal range of apparently healthy individuals, who had presented to the ER, and were further hospitalized in one of the internal medicine departments of our medical center. Exclusion criteria included a laboratory-proven viral diagnosis, a possible alternative diagnosis, patients who did not meet sepsis criteria upon admission, hospitalization within the last 7 days, and a fungal infection. A flow chart of the selection procedure is shown in Figure 1.

2.3.2. The control. We analyzed data from the Tel Aviv Medical Center Inflammation Survey (TAMCIS), a registered data bank of the Israeli Ministry of Justice.[10–14] This is a large cohort (n = 17,274) of apparently healthy individuals who attended our medical center for a routine annual check-up, and gave their written informed consent to participate. The study was approved by the local Ethics Committee (number 02-049). Data were collected between January 2004 and November 2017 due to the fact that real-time on-line wide range (wr)-CRP testing was introduced to our Medical Center only during January 2004.

2.3.3. Laboratory methods. wr-CRP measurements were done by ADVIA 2400, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA. The ADVIA Chemistry wr-CRP method measures CRP in the serum and plasma by a latex-enhanced immunoturbidimetric assay. It is based on the principle that the analytic 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. Following agglutination there is an increase in turbidity, which is measured at 571 nm. CRP concentration in the serum is determined from a calibration curve. This method measures the wr-CRP concentration range of 0.03- [156–164] mg/L. When the measured concentrations exceed 160 mg/L a dilution of 1:4 is performed.[13]

2.4. CRP velocity calculation

The time between symptom onset and the first admission CRP measurement was an approximation based on what was written in each patient's file. CRP velocity was calculated as the CRP difference divided by the hours between the 2 tests.[15] The first velocity was a rough estimation since the exact timing of the onset of fever or other symptoms was not always available. For the purpose of calculation, we took the first day as 24 h, the second as

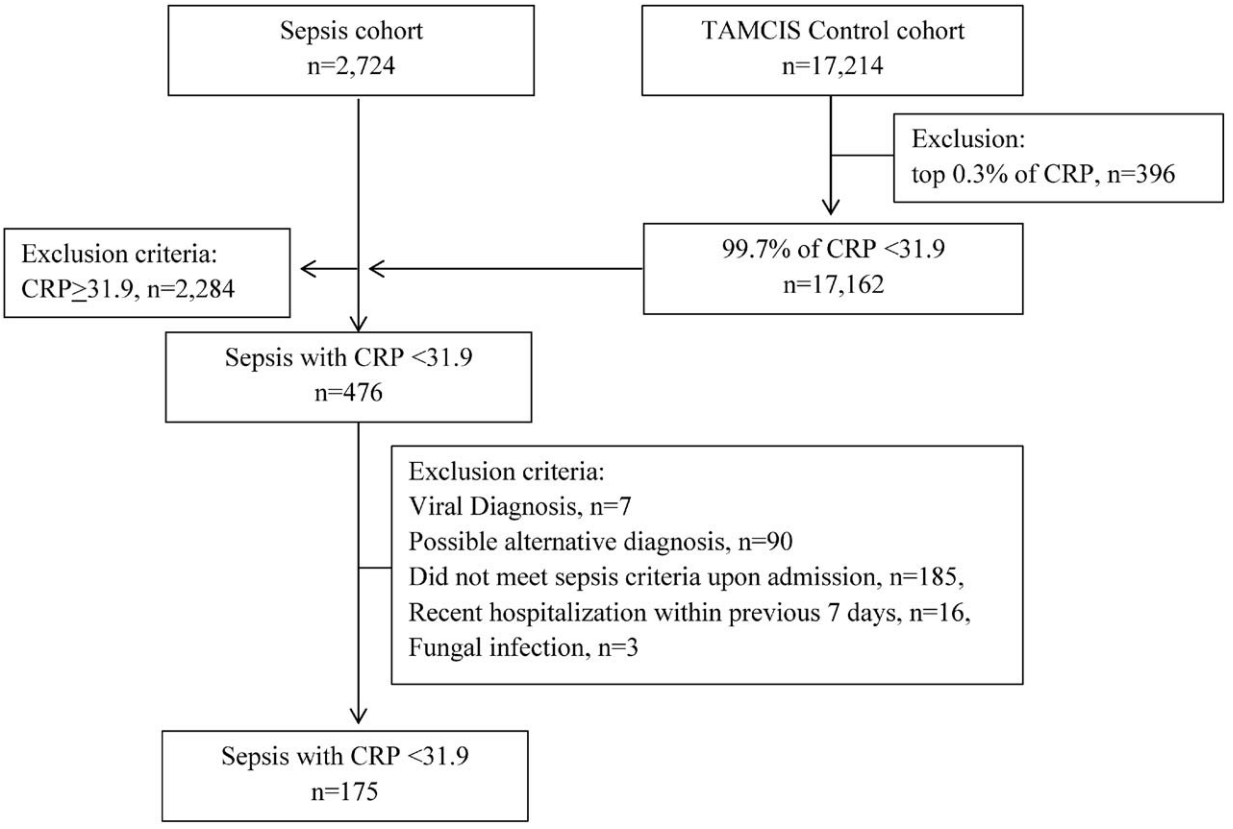

Figure 1. Flow chart of the study and subjects' selection procedure.

48. The second CRP velocity was an exact calculation because the timing of the test was obtained from the biochemistry laboratory where all the information is precise having been obtained from an automatic analyzer.

2.5. 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. Kaplan-Meier analysis was used to assess survival for 7 and 30 days from hospitalization. Spearman correlation analysis was performed in order to correlate between admission CRP, admission CRP velocity and 2nd CRP measurement. A 2-tailed P value $< .05$ was considered 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

We analyzed a total of 175 septic patients and compared their CRP concentrations as detected in the ER to those obtained from the control group of patients.

The CRP distribution in our control cohort of apparently healthy individuals (n = 17,214) was abnormal with a right tail (Fig. 1). The median CRP was 1.2 mg/L (IQR 0.40- 3.35). For the purpose of this study, we chose the 99.7 percentage of the CRP value of the control cohort to represent the upper limit for CRP in the apparently healthy population (CRP $\leq$31.9 mg/L).

Our sepsis cohort included 175 confirmed septic patients with CRP below the uppercut point of controls. The overlay CRP concentration of patients and controls is shown in Figure 2.

Most of the patients (50%) were diagnosed as having sepsis caused by a urinary tract infection, with the second leading cause being pneumonia (24%). Other sources for sepsis, including endocarditis, and cellulitis meningitis, are presented in a pie chart (Fig. 3). Eighteen patients had active malignancies. Microbiological isolation was confirmed in 32.8% of our cohort, gram-positive (GP) bacteria accounted for 9.8%,and gram-negative (GN) bacteria accounted for 22.4% of the cases. One patient had mixed (GP/GN).

Fifty-one patients (29.3%) died during the 30 days of follow-up, and 34 (19.4%) died within 7 days from hospitalization. A Kaplan-Meier plot of survival analysis is shown in Figure 4.

We were able to determine the estimated time of symptom onset in 159 (90.9%) patients. Ninety-three patients (53.1%) arrived at the ER within a few hours of symptom onset. We

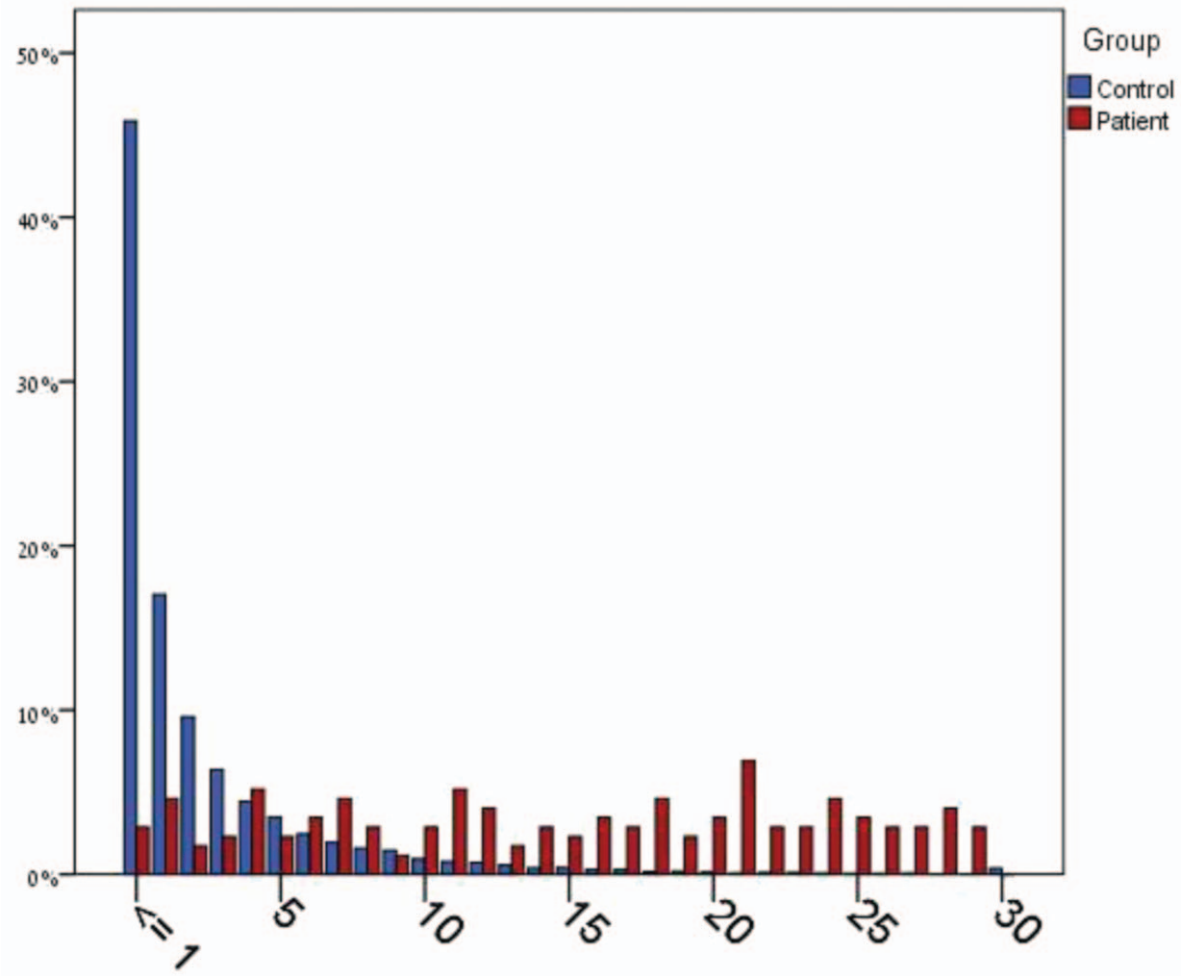

Figure 2. Similar distribution of CRP in our selected septic patients and controls. Note the large area of overlap between the groups.

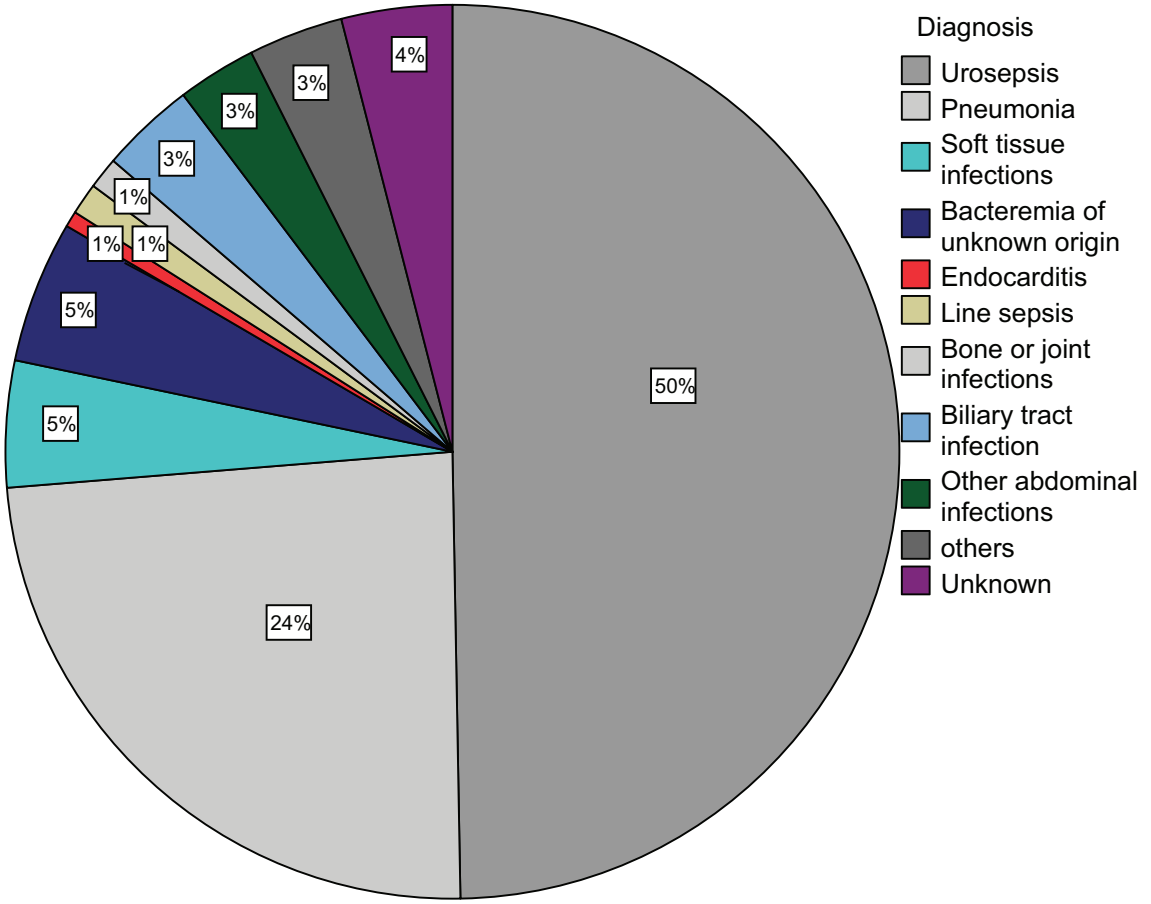

Figure 3. Main causes of sepsis were urinary tract infection, pneumonia, bacteremia of unknown origin and soft tissue infections.

completed a subgroup analysis on the remaining number of patients who arrived at the ER >12 h from symptom onset. Fourteen patients, who were treated with antibiotics prior to hospital arrival, were excluded from the study. The time difference between the 2 CRP measurements was <24 h. We found that the mean admission CRP velocity was 0.4 ± 0.29 g/L/h, and the 2nd CRP velocity was 8.3 ± 24.2 mg/L/h. No correlation was found between the absolute admission CRP concentration during admission and the 2nd CRP measurement (r = 0.085, $P = .533$). However, the admission CRP velocity was positively and significantly correlated with the 2nd CRP measurement (r = 0.383, $P = .003$, Fig. 5).

4. Discussion

To the best of our knowledge, this is the first study to document the possibility that septic patients, with an almost 20% seven-day in-hospital mortality rate, will present to the ER with a CRP concentration, which is completely within the same range as that detected in apparently healthy individuals in the community. This observation is especially relevant since sepsis could present with a clinical picture that does not always convey the immediate grave prognosis of these individuals. In fact, relatively low CRP concentrations might give the ER physician an erroneous impression regarding the severity of the disease.

The second observation of clinical relevance is the second CRP measurement taken within < 24 h, the velocity of which was significantly higher than the first.

We have previously reported regarding the possibility of using the kinetics of the CRP to reveal the evolving cytokine release during acute bacterial infections.[15] Our present findings confirm the efficacy of a second CRP to detect this release, which is not necessarily observed when a patient presents with a CRP concentration that is within normal limits.

The present observation regarding the first versus the second CRP velocity is somewhat limited by the fact that we could not retrieve the exact timing of symptom onset from the files, but obtained only a rough estimation that was categorized into 1, 2, and 3 days, etc. One could argue therefore that the first CRP velocity could not be calculated with the same precision as the second, where the timing was accurate. However, it is obvious that if a patient presents with a low CRP concentration following three days of an acute febrile illness, the velocity is low compared to the remarkable change that is detected a few hours later.

The significant change in velocity following admission to the ER might be of interest. In fact, almost 98% of the patients received intravenous antibiotics within a short period of time following ER admission. It is possible therefore that the enhanced post-antibiotic CRP velocity is a result of bacterial death and an inflammatory response to the removal of biological debris of the disintegrated bacteria, a Jarisch-Herxheimer-like response.[16] However, another possibility is that the bacterial death could be associated with less immune paresis. In this regard, we observed more mortality, albeit insignificant, in those patients who did not significantly increase their CRP concentration following antibiotic treatment (data not shown). Noteworthy is the observation

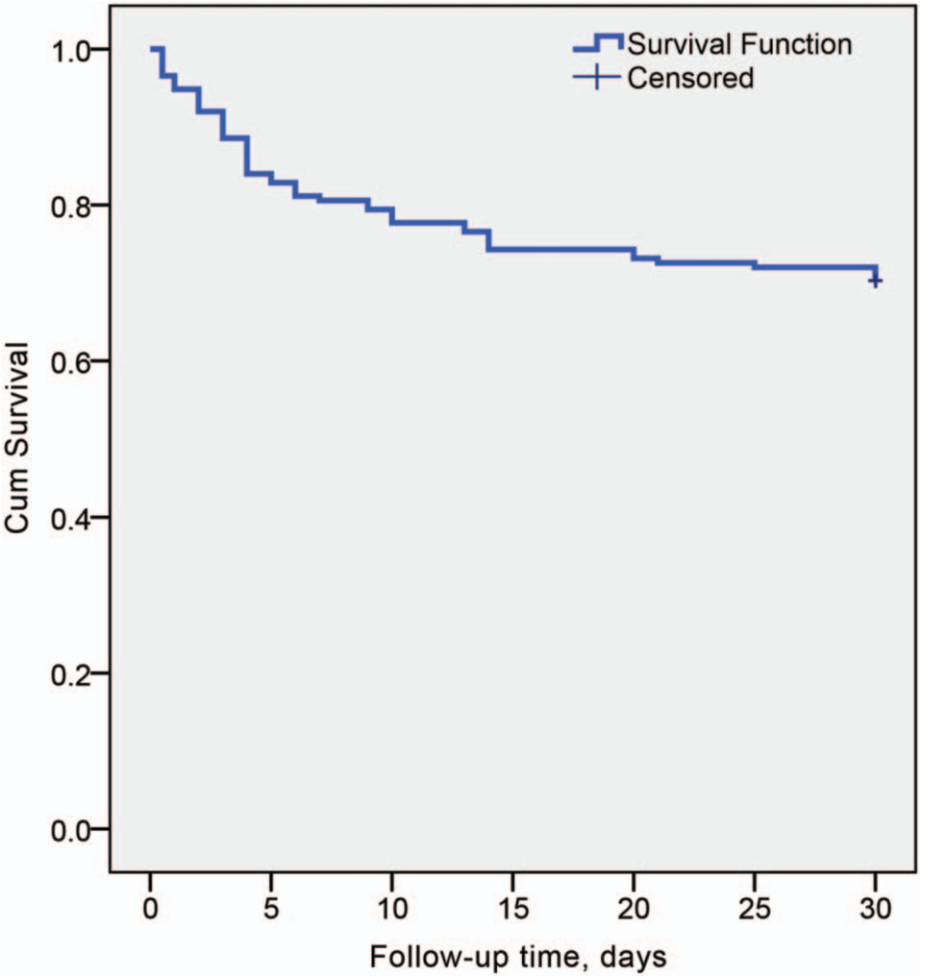

Figure 4. Kaplan-Meier survival analysis of sepsis patients with CRP below normal values.

that a correlation exists between the pre- and post-antibiotic CRP velocity, suggesting the possibility that the degree of immune paresis might also affect the magnitude of the post-antibiotic inflammatory burst.

There are several definitions of sepsis in the literature. In the present study, we have chosen the recent one,[9] but it is clear that other definitions could change somehow the inclusion of the patients but probably not the main results of the study. In addition, we did not correct the CRP results for different background diseases of our cohort since we felt that this is a too small cohort for such a purpose. It is possible though, that different background diseases like Diabetes Mellitus, liver diseases etc. might have some influence on the results.

A strength of the present study is the fact that it included patients who were admitted to the hospital despite the low CRP concentrations upon admission suggesting indeed the fact that ER clinicians should not necessarily take into consideration a first low CRP as a signal of a relatively mild infection. Moreover, we suggest that a second CRP measurement within 24 h from admission can be of clinical value.

Almost half of the patients presented to the ER within several hours from symptom onset, explaining, at least in part, the relatively low CRP concentration, an additional possibility being immunomodulation that has been described in septic patients.[7,8]

In the present study we did not intend to clarify whether CRP is a biomarker of sepsis since this is a totally nonspecific marker of inflammation. Our principal aim was to determine the magnitude of low CRP in patients with sepsis. In order to focus on a relatively homogenous population, we excluded infections that are due to nonbacterial etiologies and especially due to the fact that most septic conditions in hospitalized patients are due to bacterial infections.

Multiple biomarkers can be used in clinical medicine to establish the presence of acute bacterial infections and they include the white blood cell count as well as the differential count, Procalcitonin etc. Yet the white blood cell count and differential can be influenced by the stress condition, and especially in the ER and procalcitonin is not used, to the best of our knowledge in most hospitals as a real-time online and low-cost test.

A clinical implication of the present study is our suggestion that ER physicians ignore low CRP concentrations while facing patients with a suspected septic condition on the basis of the diagnostic workup and the question of whether the patient has a severe or a less severe illness. In addition, we show, for the first time, the potential clinical application of a second CRP test performed following antibiotic treatment and within a time frame of 24 h, in order to disclose a significant cytokine response.

We report significant CRP velocity following early (<24 h) antibiotic treatment in the ER in septic patients who present with

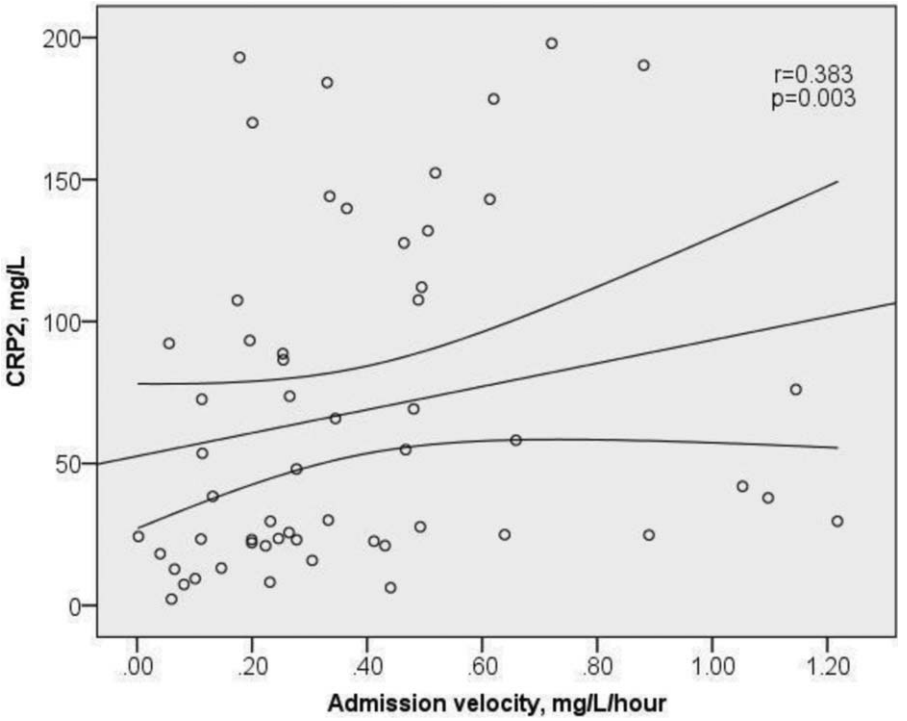

Figure 5. A significant correlation between the admission CRP and the second CRP obtained within the first 24 h of admission to the ER.

CRP concentrations that are completely within the same range as those detected in apparently healthy individuals in the community. These findings might be of particular relevance to ER clinicians, in light of the high (7-day) mortality rate observed in these patients.

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