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ORIGINAL RESEARCH

Association of Urine Levels of C-Reactive Protein with Clinical Outcomes in Patients with Pneumonia: A Pilot Study

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Abstract

Finding relevant biomarkers as a potential predictor of severity for patients hospitalized with community acquired pneumonia (CAP), in addition to the clinical scoring system, could advance progress towards more effective patient management. The inflammatory marker, C-reactive protein (CRP), which is elevated in the pathogenesis of many infectious diseases, may be a key biomarker target for CAP. Previous studies have shown that serum CRP may be a useful diagnostic marker for pneumonia in hospitalized patients with acute respiratory symptoms. The main aims of this study were to determine the correlation between serum and urine CRP levels in hospitalized patients with CAP, and any correlation with patient outcomes. Our laboratory employed a commercially available human high sensitive CRP ELISA kit to check the level of CRP in the corresponding patient urine sample. The results showed that there was a positive correlation between patient serum and urine CRP levels. In addition, we showed the correlation of urine CRP levels with certain patient comorbidities, time to clinical stability, length of patient hospital stay, and mortality.

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Introduction

Community acquired pneumonia (CAP) is a common and serious illness. Most CAP patients are treated in outpatient facilities and only 20% of CAP patients require hospitalization [1]. Among hospitalized CAP patients, the majority of deaths occur during the early days of hospitalization [2]. Early recognition of severity of CAP is essential for initiation of appropriate empiric antibiotic treatment, aggressive diagnostic work-up, and adequate supportive care. Management strategies for CAP patients depend on the severity of CAP and risk of mortality. In patients with severe CAP, a respiratory specimen does not always yield a positive microbiological culture or definitive pathogen. Furthermore, there is no single factor which can predict the severity of CAP [3].

Physicians frequently use scoring systems to assess the severity of disease and to predict likely clinical outcomes [4]. However, these scores have limitations, including age of the patient, failure to account for certain comorbidities, and other social factors [5]. These limitations have led to exploring the use of biomarkers to improve clinical management of patients with CAP. To aid clinicians in predicting risk and to treat patients with CAP, biomarkers can provide rapid information [3] and supplement accepted clinical scoring systems. Biomarkers provide quantitative information which is easy to interpret, reliable and reproducible. One of the biomarkers used to predict clinical outcomes is C-reactive protein (CRP).

CRP is named for its ability to interact with C-polysaccharide within the cellular wall of *Streptococcus pneumoniae* [6], and this interaction labels them for opsonization. CRP is an acute phase protein which is predominantly synthesized by the liver [7] in response to inflammatory cytokines IL-6, IL-1β or TNF-alpha [8], particularly in response to infection and tissue injury. These inflammatory cytokines are produced by macrophages and monocytes to destroy the pathogens at the site of infection or injury. CRP has a half-life of 19 hours in plasma [9]. Once the inflammatory stimulus is removed, the CRP level decreases rapidly. Several studies have documented that the serum CRP level serves as a good marker for diagnosis of CAP and predicts clinical severity of disease [10, 11], although the absolute CRP levels used for clinical decisions vary considerably. For conventional serum CRP assays approved by FDA [12], however, the typical cutoffs are broken out in in the following manner: healthy individuals: less than or equal to 5 mg/L, Acute range: 20-500 mg/L.

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Despite the evidence supporting use of CRP as a biomarker, there are no studies to our knowledge documenting a correlation between blood and urine CRP levels; thus, a highly sensitive CRP assay was chosen for urine sample testing since expected levels were completely unknown. In addition, there was no established relationship between CRP levels and key outcomes for patients hospitalized with CAP.

The primary objective of this initial laboratory study was to define the relationship between serum and urine CRP levels in patients hospitalized with CAP. The secondary objectives were to 1) analyze the relationship between CRP levels and clinical data, and 2) define the relationship between CRP levels and clinical outcomes of patients hospitalized due to CAP.

Materials and Methods

Study design and study population

This was a secondary data analysis of the University of Louisville's two large pneumonia studies, prospective population-based cohort studies of all hospitalized adults with CAP who were residents in the city of Louisville, Kentucky, from June 1st 2014 to May 31st 2016 (University of Louisville IRB Numbers 11.0613 and 13.0408) [13]. Patients were enrolled if they meet inclusion criteria for diagnosis of CAP.

Inclusion criteria

A diagnosis of CAP required radiographic criteria, clinical criteria and initiation of antibiotics within 24 hours of admission.

- Radiographic criteria: A new pulmonary infiltrate on imaging (computed tomography or chest x-ray) at the time of admission.
- Specific clinical signs: included new or increased cough, fever > 37.8°C (100.0°F) or hypothermia <35.6°C (96.0°F) or change in serum white blood cells (leukocytosis >11,000 cells/mm^3, left shift >10% band forms/microliter, or leukopenia < 4,000 cells/mm^3).

Urine was collected from patients once they were enrolled in study in the University of Louisville Pneumonia study [13]. Among these enrolled patients, patients with documented serum CRP in first 24 hours of hospital admission in medical record were included in this study.

Study Outcomes

Study outcomes analyzed in this study included length of stay (LOS), time to clinical stability (TCS) and mortality. Time to clinical stability was defined as the day patient met the following four criteria: (1) improvement in cough and shortness of breath, (2) lack of fever for at least 8 hours, (3) improved leukocytosis and (4) tolerance to oral intake. Patients were evaluated daily for first seven days of hospitalization to determine the day when clinical stability was reached; however, patients still unstable at day seven were censored at eight days. Length of stay was defined as number of days from admission to discharge. Patients hospitalized for more than 14 days were censored at 14 days. Mortality (any cause) was evaluated from admission to up to one year after admission.

Patient Groupings

The samples used in this preliminary study were selected based on patient serum CRP levels obtained from hospital records. The serum CRP level was collected within the first 24 hours of hospitalization. The urine samples from patients were collected after enrollment within the first 48 hours of hospitalization. The urine samples were divided into three groups: low, intermediate and high according to serum CRP levels (1-10 mg/L, 11-50 mg/L, 51-270 mg/L, respectively) (Figure 1A). Processing and storing of the urine samples can be found in the "Sample Selection" section. There were ten consented patient urine samples included in each CAP group, plus consented healthy volunteers provided urine samples that were used as controls (no CAP). Supplemental information for all pneumonia patients is included in **Table 1**.

Sample processing and selection

Archived urine samples from University of Louisville Respiratory Specimen Biorepository in the Division of Infectious Diseases were used. Urine specimens selected for this study were collected from July 2014 to January 2016 [13] under IRB Numbers 11.0613 and 13.0408. Briefly, the original urine samples from patients hospitalized with CAP were held at 4°C, then processed within 28 hours of collection by adding 0.5 mL of 0.5 M PIPES buffer (VWR, Radnor, PA, part number BB-121-250 mL) to 9.5 mL of urine. After mixing well, aliquots were frozen at -80°C until thawed. Next, 1 mL of thawed urine sample was centrifuged at 300x*g* for 5 minutes and 240 μL of supernatant was aliquoted into each of four tubes for this study. These aliquoted samples were frozen at -20°C until thawed for the enzyme-linked immunosorbent assay (ELISA) described below. The same urine processing protocol was followed for urine samples from healthy volunteers. All samples were tested undiluted (raw) in duplicate and the ELISA was repeated three times independently.

Human highly sensitive enzyme-linked immunosorbent assay for C reactive protein (CRP-ELISA)

The human high sensitive CRP-ELISA was obtained from MyBioSource, Inc. (Research Use Only, Cat. No: MBS2021863, San Diego, CA). Urine samples were thawed, and brought to room temperature prior to using 100 μL of raw urine. The sandwich ELISA assay was performed following the manufacturer's instructions. Briefly, blanks and standards were included in each run by adding 100 μL of each dilution of standards and blanks, as well as samples (in duplicate) into the appropriate wells. After covering the plate and incubating for one hour at 37°C, the samples were removed manually and 100 μL of Detection Reagent A were added (biotin-conjugated antibody specific to human CRP). After re-covering the plate, incubation proceeded for one hour at 37°C. Detection Reagent A was removed and wells were washed three times manually with wash buffer. Next, 100 μL of Detection Reagent B (avidin-conjugated horseradish peroxidase) was added to each well. The plate was again covered and incubated for 30 minutes at 37°C. Detection Reagent B was manually removed and all wells were washed five times manually with wash buffer. Finally, 90 μL of TMB substrate solution (3,3',5,5'-Tetramethylbenzidine) was added to each well, and the plate was covered and incubated 10-20 minutes at 37°C, protected from light. The stop solution was added, changing the color from blue to yellow, and the plate was read at 450 nM using a spectrophotometer. The unknown urine sample concentrations were determined by extrapolating from standards run on the same plate on the same day. The minimum detectable amount of CRP is typically less than 23.3 pg/mL. This assay has high sensitivity and excellent specificity for detection of human CRP, noting that a CRP concentration above 4000 pg/mL was outside the linear range of the ELISA.

Table 1. Supplemental Information for Pneumonia Patients: Clinical Features

Variable	High	Intermediate	Low	*p*
n	10	10	10	
Demographics				
Age (median [IQR])	70 [64-78]	59 [50-78]	66 [52-76]	0.577
Male Sex (%)	3 (30)	7 (70)	7 (70)	0.114
Black Race (%)	2 (20)	1 (10)	0 (0)	0.329
Social/Medical History (n (%))				
Obese	1 (10)	6 (60)	4 (40)	0.065
Hx HIV	0 (0)	1 (10)	0 (0)	0.355
Hx Neoplastic Disease	1 (10)	3 (30)	1 (10)	0.383
Hx Renal Disease	2 (20)	3 (30)	2 (20)	0.830
Hx CHF	3 (30)	0 (0)	3 (30)	0.153
Hx COPD	3 (30)	4 (40)	3 (30)	0.861
Hx Stroke	0 (0)	1 (10)	2 (20)	0.329
Hx Liver Disease	2 (20)	0 (0)	2 (20)	0.315
Hx Diabetes	5 (50)	4 (40)	4 (40)	0.873
Smoking History				0.482
Current	2 (20)	2 (20)	5 (50)	
Former	5 (50)	4 (40)	2 (20)	
Never	3 (30)	4 (40)	3 (30)	
Cardiovascular Risk Factors and Medications (n (%))				
Family Hx CAD	5 (50)	0 (0)	3 (30)	0.039
Active CAD	4 (40)	2 (20)	5 (50)	0.366
Arterial Hypertension	7 (70)	7 (70)	8 (80)	0.843
Hyperlipidimia	6 (60)	3 (30)	8 (80)	0.076
Hx Prior MI	2 (20)	2 (20)	3 (30)	0.830
Hx Prior PCTA	3 (30)	1 (10)	4 (40)	0.303
Atrial Fibrillation	1 (10)	1 (10)	2 (20)	0.749
Asprin Use	5 (50)	4 (40)	3 (30)	0.659
Beta Blocker Use	4 (40)	3 (30)	6 (60)	0.387
Ace Inhibitor Use	2 (20)	3 (30)	2 (20)	0.830
Warfarin Use	1 (10)	0 (0)	2 (20)	0.329
Heparin Use	1 (10)	0 (0)	0 (0)	0.355
Antiplatelet Use	1 (10)	0 (0)	1 (10)	0.585
Statin Use	5 (50)	4 (40)	3 (30)	0.659
Physical Exam and Laboratory Findings (median [IQR])				
Temperature (degrees Celsius)	38 [37-38]	37 [37-38]	37 [37-37]	0.150
Respiratory Rate (breaths/min)	22 [20-24]	22 [18-24]	19 [16-24]	0.535
Heart Rate (beats/min)	106 [97-124]	116 [106-123]	81 [72-102]	0.024
Systolic Blood Pressure (mmHg)	108 [98-116]	118 [109-141]	134 [122-158]	0.020
Diastolic Blood Pressure (mmHg)	54 [46-66]	59 [52-68]	74 [63-92]	0.109
Bicarbonate (mEq/L)	28 [25-29]	24 [22-25]	26 [25-26]	0.067
Blood urea nitrogen (mg/dL)	14 [12-27]	24 [18-29]	16 [11-20]	0.159
Glucose (mg/dL)	143 [123-176]	197 [130-271]	104 [102-130]	0.057
Hematocrit (Percent)	30 [28-34]	38 [30-42]	35 [33-44]	0.136
Sodium (mEq/L)	136 [136-139]	136 [130-140]	138 [134-139]	0.775
Severity of Disease (n (%))				
Direct admission to ICU	1 (10)	1 (10)	1 (10)	>0.999
Altered mental status	3 (30)	1 (10)	4 (40)	0.303
Need for vasopressors	0 (0)	0 (0)	0 (0)	>0.999
Need for ventilatory support	0 (0)	1 (10)	1 (10)	0.585
PSI* Risk Class IV-V	8 (80)	4 (40)	5 (50)	0.171

*Pneumonia Severity Index

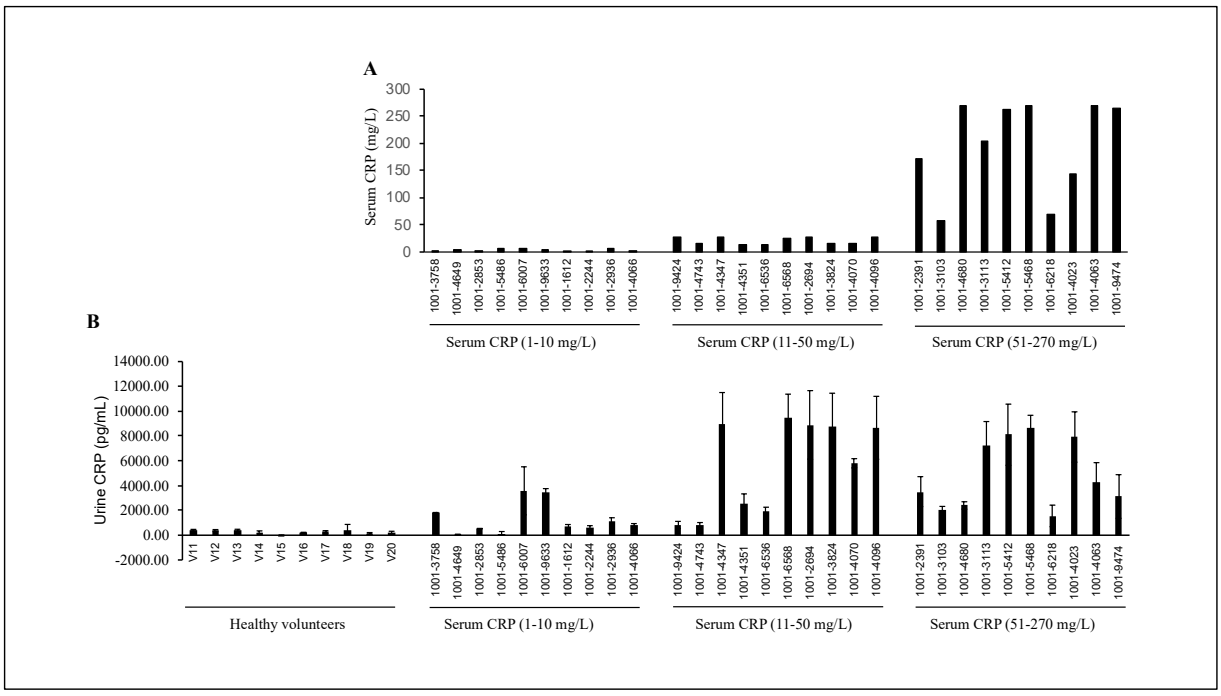

Figure 1. CRP level of pneumonia patients. A) Level of serum CRP on pneumonia patients. Using data obtained from hospital records, these pneumonia patients' urine samples were divided into three groups according to serum CRP levels, each group having 10 patients assigned a unique subject identification number (Serum CRP 1-10 mg/L, 11-50 mg/L, 51-270 mg/L). **B) Level of urine CRP on healthy volunteers and pneumonia patients.** Urine samples from 10 healthy volunteers and 30 pneumonia patients were tested using a human highly sensitive enzyme linked immunosorbent assay for C-reactive protein (CRP). All samples were run duplicate in each ELISA, and the values shown represent mean ± SD from three independent experiments.

Statistical Analysis

Simple linear regression was performed to define the relationships between serum CRP and urine CRP. Laboratory values that had a p-value of less than 0.2 were identified for further investigation; Pearson and Spearman correlation was performed to analyze associations between CRP levels and laboratory values. Patient characteristics were summarized by group with descriptive statistics. Continuous data was reported as mean and interquartile range; categorical data was represented as frequency and percentage. Differences in patient characteristics were tested by Fisher's Exact test for categorical data and the Kruskal-Wallis Rank Sum Test for continuous data. Kaplan-Meier curves were created to visualize outcomes, and log-rank tests were used to compare outcomes among groups. Microsoft Excel and R version 3.5.1 were used for analysis.

Results

Clinical characteristics of the three CRP groups

The serum CRP level as collected from patient's medical record have been arranged by low, intermediate and high serum CRP level groups (**Figure 1A**). We were able to detect CRP in urine with the human CRP-ELISA in the picogram range from urine samples collected from 30 patients with CAP; note that these data were arranged by serum CRP groups (**Figure 1B**). Also, CRP levels detected in urine samples were collected from 10 healthy volunteers as controls (**Figure 1B**). All three groups of pneumonia patients show increased levels of urine CRP level when compared to healthy volunteers. Intermediate Serum CRP group showed higher level of urine CRP as compared to high serum CRP level group. Patient characteristics were collected from medical records (**Table 1**). Systolic blood pressure, heart rate, and family history of coronary artery disease were found to be significantly statistically different between CRP groups. The intermediate group had higher numbers of patients who were obese, HIV-infected, with a history of neoplastic disease or elevated blood glucose levels, but these were statistically not significant.

Relationship between serum and urine CRP

The relationship between log serum and log urine CRP was positive and linear (**Figure 2**). An increase of 1 log mg/L of serum CRP was indicative of an increase of 0.4 log pg/mL of urine CRP (β=0.4, p=0.002, R^2 = 0.29).

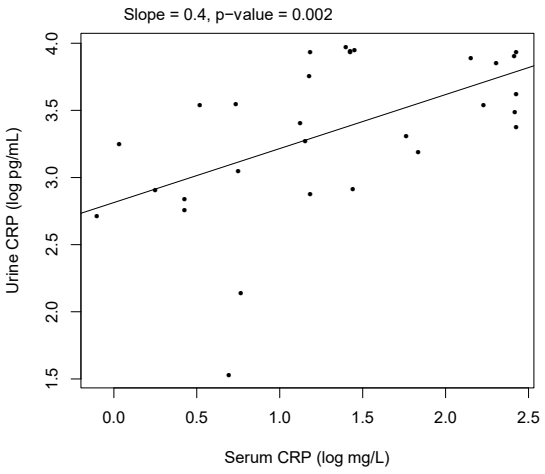

Figure 2. Association between serum and urine CRP levels. The trend line from linear regression is shown.

Correlation between CRP and other laboratory values

Laboratory values identified for follow-up analysis were temperature, heart rate, systolic blood pressure, diastolic blood pressure, serum bicarbonate, blood urea nitrogen,

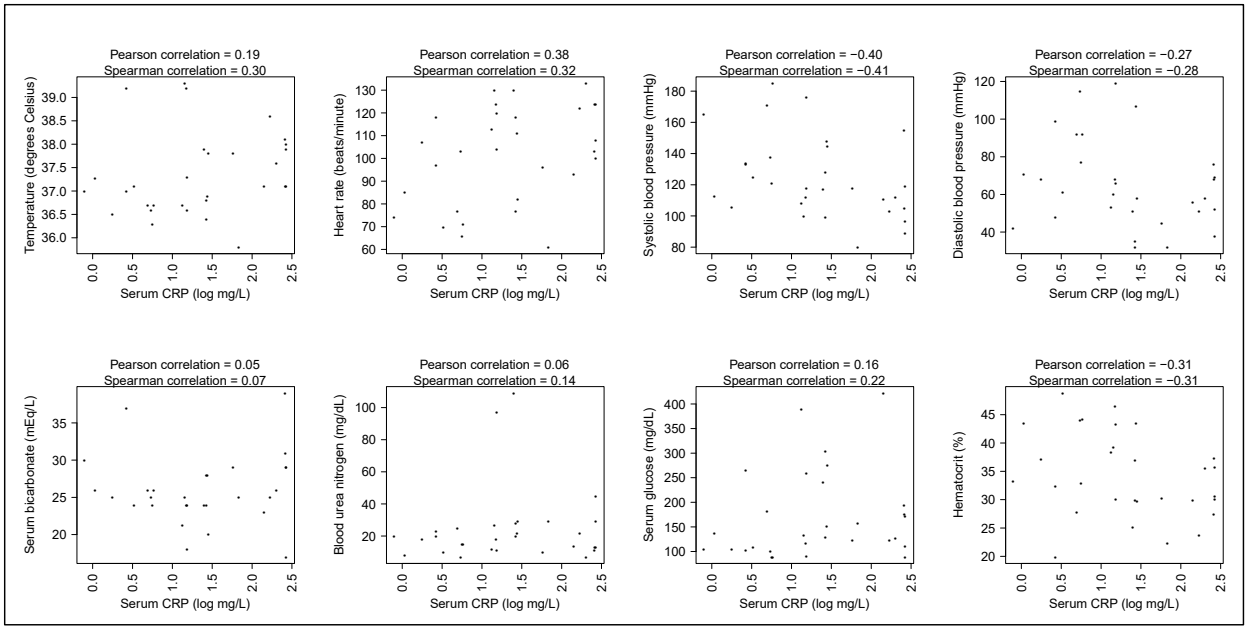

Figure 3. Associations between serum CRP and laboratory values. Scatterplots shown compare serum CRP values and other laboratory values. Pearson and Spearman correlations are shown above each respective scatterplot. After adjusting for multiple comparisons, none are significant.

serum glucose, and hematocrit. Scatterplots were produced to illustrate log serum and log urine CRP levels compared to these laboratory values (**Figures 3 and 4**). Correlations ranged from -0.42 to 0.43. After adjusting for multiple comparisons, no correlations were statistically significant.

CAP Patient Outcomes

We did not find statistically significant differences between groups for time to clinical stability and mortality at 1 year. Length of stay was found to be statistically significant between groups. Patient outcomes and statistical tests are shown in **Table 2**. Kaplan-Meier curves for time to clinical stability, length of stay, and mortality are shown in **Figures 5-7**, respectively, and summarized in **Table 2**.

Discussion

We observed increased urine CRP levels in pneumonia patients (**Figure 1B**) as compared to healthy volunteers, and there was a significant positive correlation of CRP levels between serum and urine samples (**Figure 2**). Studies have shown that markedly elevated serum CRP levels are strongly associated with bacterial infection [14]. CRP levels have been demonstrated to increase with pneumonia, confirming bacterial pneumonia in children [15, 16], as well as adult HIV-infected inpatients [17]. It has been recommended, however, to combine serum CRP values with other clinical prediction parameters to better identify patients with severe pneumonia and at risk of poor outcomes.

Many common laboratory values (such as hematocrit, glucose and blood urea nitrogen levels) were not statistically significantly correlated with either serum or urine CRP levels (**Figures 3 and 4**). TCS was not significantly correlated with CRP levels (**Figure 5**); however, the patient's LOS at the hospital increased in direct proportion to increasing CRP levels (**Figure 6**). Some possible explanations for this correlation may include the direct link between inflammation and fever due to release of pyrogens, increased circulating levels of IL-6 and IL-10 cytokines [18] or complications of inflammation that lead to longer hospital stays, such as myocardial infarctions [19, 20].

We found 50% mortality in the high CRP group, and 30% of mortality in both the intermediate and low CRP groups in the present study (**Figure 7**). While the number of patients is low in this preliminary study, increasing the number of patients in future propspective studies may increase the statistical significance of these findings. Ramirez *et al* [13] and other investigators [21-23] stated that patients hospitalized with CAP showed a higher mortality rate compared to those without CAP. Another multi-center, one-year follow-up study with patients discharged after hospitalization for CAP found elevated pro-inflammatory marker IL-6 in the circulation, and was associated with a higher mortality rate [18]. The higher mortality rate was attributed to death by cardiovascular disease and cancer [18]. It is notable that IL-6 is one of the important cytokines causing the liver to synthesize CRP [8]. CAP substantially increases the risk of heart disease across all age groups [23], so the mechanism behind this is likely multi-dimensional. Based on the aforementioned studies, increases in CRP levels could be one of the mechanisms.

Table 2. Patient outcomes

Outcome	Low CRP	Intermediate CRP	High CRP	Test statistic	p-value
Time to Clinical Stability (days) †	3 [1-4]	2 [1-3]	2[1-5]	$X^2_{(2)}$=0.5	0.800
Length of Stay (days) †	3 [1-4]	4 [2-5]	8 [5-10]	$X^2_{(2)}$=7.2	0.030
1 year mortality ‡	3 (30)	3 (30)	5 (50)	$X^2_{(2)}$=1.6	0.400

† Median [Interquartile range]

‡ Frequency (percentage)

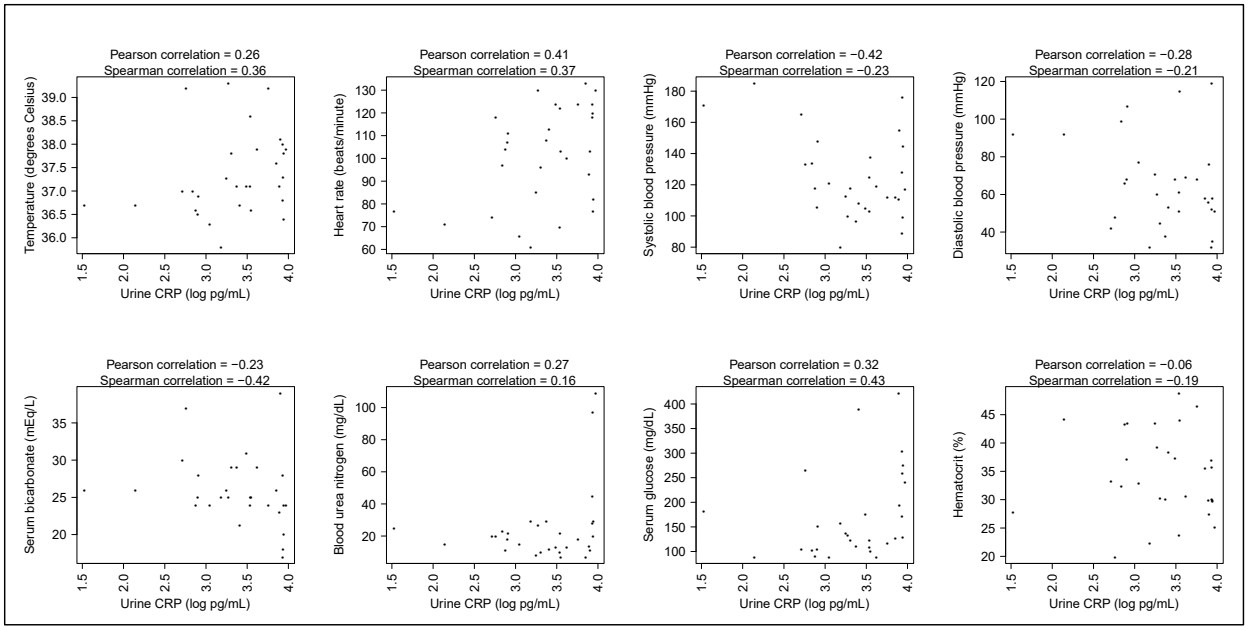

Figure 4. Associations between urine CRP and laboratory values. Scatterplots shown compare urine CRP values and other laboratory values. Pearson and Spearman correlations are shown above each respective scatterplot. After adjusting for multiple comparisons, none are significant.

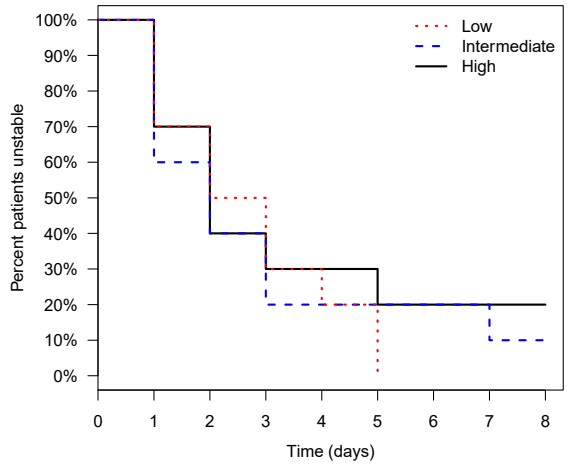

Figure 5. Kaplan-Meier curve for time to clinical stability, in days, for low, intermediate and high urine CRP levels.

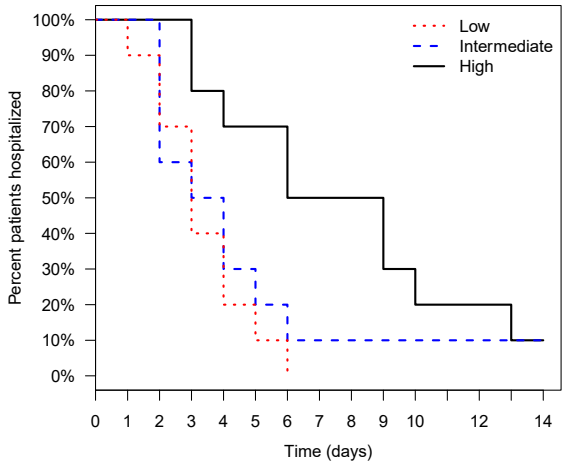

Figure 6. Kaplan-Meier curve for hospital length of stay, in days, for patients with low, intermediate and high urine CRP levels.

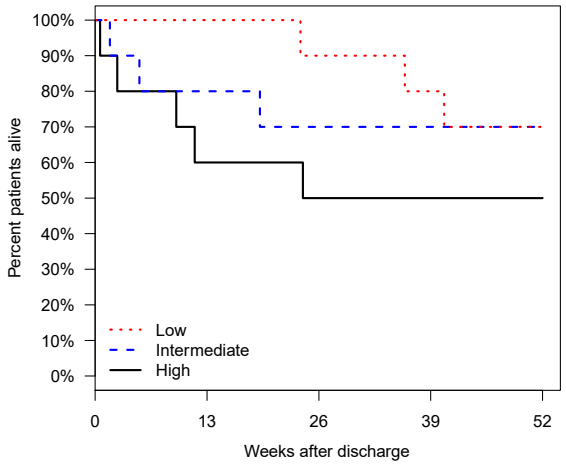

Figure 7. Kaplan-Meier curve for time to death, in weeks, for patients with low, intermediate and high urine CRP values.

To our knowledge, there have been no studies conducted to date to determine urine CRP levels in hospitalized patients with CAP. Since urine is a non-invasive specimen type for critically ill patients, this would be a novel approach for monitoring CRP levels. Other researchers studied urine CRP levels in patients with lower urinary tract symptoms (LUTS) and children with urinary tract infections (UTI), but CRP was not found to be a specific biomarker for either condition [24, 25]. In one study, they detected only one patient with elevated urine CRP level (0.86 mg/L) out of 97 patients, whereas serum CRP was elevated in different patients with LUTS [26]. A highly sensitive human CRP ELISA assay was used in this present study because urine CRP levels were unknown, and no other studies used this particular ELISA assay on urine samples. Unfortunately, there is no urine CRP measurement kit available for *in vitro* diagnostics, and commercially available kits are for research use only (RUO). The use of the highly sensitive human CRP ELISA was both a strength and a limitation of this study, allowing us to detect low quantities of CRP but creating difficulties when comparing results from other urine studies. While using archived, processed urines was necessary for this pilot study, the use of fresh urine specimens would be an improvement. Another weakness of the study was the number of patients in each group, limiting the statistical power when comparing groups.

A future prospective study with increased number of patients is needed for a variety of reasons. These reasons, along with goals for future studies, include the following:

1) to increase the number of enrolled patients to reach statistical significance in some of the outcomes measured. For example, in patients with increased CRP levels, we would most likely observe more cardiovascular events and mortality in the long term follow up.
2) to definitively validate the use of urine CRP level as a biomarker for poor outcomes in CAP patients, lending the test to development of point of care or at-home test for urine CRP.
3) to plan interventional studies using urine CRP levels to monitor the effect of anti-flammatory (steroids and/or cytokine-specific biologics) agents with standard antibiotic therapy in the treatment of hospitalized patients with CAP.
4) to define if certain antibiotics with anti-inflammatory properties (such as macrolides or teracycline) may add some benefit in terms of clinical outcomes, particularly with regard to cardiovascular morbitidy and mortality.

In these aforementioned future studies, we can determine if less inflammation ultimately increases the survival rate. If the data trends from the pilot study hold true in larger prospective studies, then there will be many useful applications for detecting urine CRP levels in patients with CAP. From the laboratory perspective, the possibility of developing a point of care test for using urine to monitor CAP patients' CRP levels is exciting. For example, using a simplified, rapid urine CRP test at home for patients with respiratory symptoms could guide whether they choose to stay home or seek health care. With a point of care test in a hospital setting, a urine sample with a moderate or high CRP value would help nurses better triage patients with respiratory symptoms. In conclusion, this pilot study suggests that measuring urine CRP levels from patients with CAP could be used successfully as a biomarker for starting interventions and improving health outcomes, ultimately leading to cost savings in the health care system.

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