CRP: a biomarker for early detection of bacterial infection

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Abstract

Background: although C-reactive protein (CRP) is widely used in younger populations, its value for diagnosing bacterial infection in older population is not well established. This study examined the usefulness of serum CRP level in the early detection of bacterial infection in older patients.

Methods: in a prospective cohort study, consecutive patients aged 70 years or over admitted to Aged Care wards were recruited. CRP levels were measured within 24 h of presentation, and their significance in predicting bacterial infections was analysed. The relationship between CRP and other clinical features of diagnosing bacterial infections (e.g. temperature, white cell count, neutrophil count, oxygen saturation, blood pressure and heart rate) was also examined.

Results: a total of 232 patients were recruited over a period of 3 months. CRP levels were 21.3±36.0 and 150.5±114.1 mg/l (mean±SD) in the non-infection and infection groups, respectively (P<0.001). We found that the CRP cut-off value of 60 mg/l had the best combination of sensitivity and specificity. At this level, the sensitivity of diagnosing bacterial infection was 80.7%, specificity 96.0%, positive predictive value 91.9% and negative predictive value 89.8%. CRP and temperature had higher sensitivity and specificity than white cell count and neutrophil count in the diagnosis of infection. For every 1-mg/l increment in CRP, the risk of bacterial infection increases by 2.9%.

Conclusion: CRP is a convenient and useful biomarker to predict early bacterial infection in older patients especially when other markers are atypical or not present.

Keywords: bacterial infection, C-reactive protein (CRP), elderly, older person

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Bacterial infections are a major cause of morbidity and mortality in the elderly population in hospitals [1–3]. The elderly patient is generally susceptible to infections because of a decline in host defence mechanisms that occurs with ageing, and concomitant medical co-morbidities [1–3]. The most common infections of the elderly are respiratory tract infection, urinary tract infection, and skin and soft tissue infections [4]. However, the clinical manifestations of infections in the elderly patient are usually atypical. Tachycardia, tachypnoea, hyper/hypothermia, hypotension, hypoxaemia and leucocytosis are not always present in elderly patients with sepsis [4]. Hence, recognition and diagnosis of bacterial infections can be challenging particularly in the early phase of infection. Nevertheless, prompt diagnosis of infections allows early implementation of antibiotics which can prove critical to long-term outcomes [5]. In addition, it would also reduce unnecessary administration of antibiotics in the case of non-infections and, indirectly, the spread of antibiotic-resistant organisms.

Intuitively, a biomarker that can predict bacterial infections with reasonable sensitivity and specificity will enable early diagnosis of sepsis, thereby improving patient’s clinical outcomes, and reducing morbidity and mortality [3].

C-reactive protein (CRP) is an acute phase protein produced by the liver. Plasma concentrations are normally under 10 mg/l, but this may increase several fold after a physical trauma [6]. Bacterial infection is also a potent stimulus, leading to rapid elevation of CRP levels within hours [6]. It is also known that there can be sustained CRP elevation with active inflammatory disease. Other factors that associate with elevated CRP include pulmonary embolism, deep vein thrombosis, myocardial infarction, malignancies, rheumatoid arthritis and autoimmune diseases (including vasculitis). Interleukin 6 (IL-6) is thought to be the main mediator stimulating CRP production, but other cytokines like IL-1 and tumour necrosis factor are also involved [7, 8]. Changes of plasma CRP levels have been shown to be useful in the diagnosis of infection [9–17] and in the follow-up of the clinical course of infection, with a fall in CRP usually accompanying resolution of the disease [9–17]. Unfortunately, most of these studies were carried out in the critical care settings, and in younger adults or paediatric patients [9–18]. A few more studies have also shown an added value of CRP in an outpatient setting, systemic inflammatory response syndrome (SIRS) and periodontal infections [19, 20]. Nevertheless, the usefulness of elevated CRP in early diagnosis of bacterial infection in the elderly population has not been well established. In the studies of Povoa et al. [9] and Yentis et al. [10], the patients were recruited in the intensive care setting with an average age of 61.3 ± 17 years. The number or proportion of patients older than 65 years old was not available. In the studies of Cox et al. [11] and Kenny et al. [18], the authors did not specifically examine the diagnostic properties of CRP. The former study examined the pattern of CRP response in infections, while the latter showed that the mean level of CRP is much higher in the elderly with septicemia [11, 18]. Despite this, as CRP assay is fast, readily available and inexpensive, it has been variably utilised in most hospitals and community settings [11–20], but in some centres such as ours, CRP is not a routine screening test for bacterial infection. Therefore, the principal aim of this study was to evaluate the usefulness of initial serum CRP level, both in isolation and in combination with other clinical and biochemical parameters of infection in the early detection of bacterial infection in Aged Care patients admitted to the hospital via Emergency Department.

Methods

Subjects

This was a prospective cohort study carried out at Bankstown–Lidcombe Hospital (Sydney, Australia). As this was a pragmatic study, over a period of 3 months from October to December 2008, consecutive patients admitted under the care of all four Aged Care teams (via Emergency Department) were prospectively included in the study. We excluded the following: (i) patients aged less than 70 years old, (ii) lack of consent from the patients or their legal proxies as defined by New South Wales Guardianship Act 1987 Section 33A, (iii) patients who have been discharged from the hospital within 24 h and (iv) patients with severe clinical illness in the setting of multiple and/or non-reversible co-morbidities where comfort care (as determined by their clinicians) is the most appropriate rather than active antibiotic therapy.

Definition of bacterial infection

Patients’ infection status was defined according to the International Sepsis Definition Conference (ISDC) 2001 [21].

- Definite infection—patients with definite infection established on clinical and microbiological criteria.
- Probable infection—patients with clinical manifestation of infection plus radiological evidence without microbiological confirmation.
- Possible infection—patients with clinical features of infection without established microbiological or radiological confirmation.
- Non-infection—defined as no clinical, microbiological or radiological evidence of bacterial infection.

Data collection and CRP measurement

All subjects had CRP measured within the first 24 h of admission. The serum samples for CRP were collected without anticoagulation. The specimen were then centrifuged at 3,000 rpm for 10 min, and the CRP levels were estimated in the same day by means of the VITROS® 5,1 FS Chemistry System automated immunoturbidimetric method (Medcompare™). The method has a lower limit of sensitivity (2 mg/l).
In addition, patients’ characteristics and clinical details were prospectively obtained from review of clinical notes. The data collected included patients’ age, gender and clinical markers of bacterial infection such as heart rate (HR), respiratory rate (RR), blood pressure (BP), temperature and oxygen saturation (SO₂%). We also obtained the final diagnosis of infection or non-infection (as made by the treating clinicians). Infection group was further divided into definite, probable and possible infection. Where there was ambiguity, the patients’ results were clarified with the treating teams. In addition, we reviewed the biochemical markers [e.g. white cell count (WCC), neutrophils (N) and lymphocytes (L)], microbiology results (e.g. urine culture, blood culture, wound culture, etc.) and radiological tests. All radiological findings were confirmed by radiologists.

Ethics matters

The study was approved by the local Human Research Ethics Committee, Sydney South West Area Health Service (western zone). All subjects were informed of the purpose and procedure of the study, and all gave consent to participation.

Statistical methods

Data were analysed using SPSS version 15.00 (SPSS Inc., Chicago, IL, USA). The mean CRP (95% CI) levels between different ISDC categories were calculated using the t-distribution. Differences between these four groups were further analysed using one-way ANOVA test for continuous variables and chi-square test for categorical variables. The four ISDC categories were then reorganised into bacterial infection (definite, probable and possible) and non-infection for ease of analysis and to reflect clinical management of suspected infections. Cut-off CRP values were determined by receiver operating characteristic (ROC) curve distribution. Sensitivity, specificity, positive and negative predictive values, and relative risk of acquiring bacterial infection were also obtained. Binary logistic regression method (backward LR) was then used to identify predictive factors for final diagnosis of bacterial infection. Data are presented as the mean±SD for normal distribution, and average and range for non-normal data. Two-tailed P-values <0.05 are considered to be statistically significant.

Results

Patients’ characteristics

We were able to recruit all of the eligible patients in our study. As CRP can be requested retrospectively on the initial blood specimen, additional blood collection was not required, and patient’s usual care was not affected. The basic characteristics of the patients are summarised in Table 1. There were a total of 232 patients, 135 women of average age 82.6 years (range, 70–99) and 97 men, aged 82.6 years (range 69–95). Of the 232 patients, 149 patients had non-infective causes, and 83 patients were diagnosed with bacterial infections. Among them, 34 patients had definite infection, 30 had probable infection and 19 had possible infection according to the ISDC 2001 [21]. Twelve (5.1%) of the 232 patients admitted died in the hospital; among these, six (50%) died of aspiration pneumonia. Other deaths were due to stroke, complications of advanced dementia or end-stage malignancy (full data is not shown).

The five most common diagnoses in the bacterial infection group consisted of pneumonia, inclusive of aspiration pneumonia (34.9%); cellulitis and/or infective skin ulcers (27.7%); urinary tract infection (UTI) (21.7%); infective exacerbation of chronic obstructive pulmonary disease (7.2%); and proven bacterial gastrointestinal infection (4.8%). In the non-infection group, the major diagnoses were cardiovascular diseases including heart failure (20.8%); falls and fractures (17.4%); degenerative and inflammatory joint diseases (12.0%), including two cases of gout; stroke (8.0%); renal failure (8.0%); viral upper respiratory tract infection (5.4%), and one case of viral gastroenteritis. There were no cases of tuberculosis or fungal infection.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of infection and non-infection groups</th>
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<tbody>
<tr>
<td>Age (years) (range)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Male (%)</td>
</tr>
<tr>
<td>Mean CRP ± SD (mg/l)</td>
</tr>
<tr>
<td>Mean temperature ± SD (°C)</td>
</tr>
<tr>
<td>HR ± SD (/min)</td>
</tr>
<tr>
<td>Systolic BP ± SD (mmHg)</td>
</tr>
<tr>
<td>Diastolic BP ± SD (mmHg)</td>
</tr>
<tr>
<td>SO₂ ± SD (%)</td>
</tr>
<tr>
<td>WCC ± SD (10³/l)</td>
</tr>
<tr>
<td>Neutrophils ± SD (10³/l)</td>
</tr>
<tr>
<td>Lymphocyte ± SD (10³/l)</td>
</tr>
</tbody>
</table>

HR, heart rate; BP, blood pressure; WCC, white cell count; SO₂, oxygen saturation.
CRP levels and their relationship with infection

We found that the definite infection group had higher mean temperature, HR, WCC, neutrophil count and lymphocyte count compared with the non-infection group. The former also had lower diastolic blood pressure and SO\textsubscript{2} than the latter (Table 1). Mean CRP levels were 21.3±36.0 and 150.5 ± 114.1 mg/l in the non-infection and infection groups, respectively. The mean CRP levels in the definite infection, probable infection and possible infection were significantly higher than that in the non-infection group (168.9 ± 125.3, 144.9±92.0 and 135.0 ± 116.4 mg/l, and 21.3±36.0 mg/l, respectively, \( P < 0.001 \)).

CRP cut-off values for diagnosing bacterial infection were obtained after analysing the ROC curve of all CRP samples. The values tested ranged from 30 to 80 mg/l (normal ≤5.0 mg/l) (Table 2 and Figure 1). It appeared that CRP cut-off values from 30 to 60 mg/l had a good sensitivity for diagnosing sepsis in the elderly; however, a CRP level of 60 mg/l had the best balance of sensitivity, specificity, and positive and negative predictive values (Table 2). The ROC curve analysis was also performed for temperature, WCC and neutrophil count. CRP and temperature had higher sensitivity and specificity for diagnosing infection than WCC and neutrophil with areas under the curve (AUC) of 0.920 and 0.815 versus 0.689 and 0.695, respectively (Figure 1).

The relationship between clinical features, biomarkers (including CRP) and bacterial infection was analysed using binary logistic regression models. There was no correlation between the diagnosis of bacterial infection with mean systolic and diastolic blood pressure, oxygen saturation, and heart rate (results not shown). However, individually, there was a significant correlation between CRP level, temperature, WCC and neutrophil count with the diagnosis of infection. Therefore, backward logistic regression method was used to identify predictive factors for the final diagnosis of bacterial infection based on these four items (see Table 3). CRP and temperature were the strongest predictors of bacterial infection, whereas the relationship between WCC, neutrophil count and infection became less significant.

### Table 2. CRP cut-off values in diagnosing infection

<table>
<thead>
<tr>
<th>CRP cut-off scores</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>86.7</td>
<td>81.2</td>
<td>72.2</td>
<td>91.6</td>
</tr>
<tr>
<td>40</td>
<td>83.1</td>
<td>87.9</td>
<td>78.2</td>
<td>90.2</td>
</tr>
<tr>
<td>50</td>
<td>82.7</td>
<td>91.3</td>
<td>84.2</td>
<td>90.4</td>
</tr>
<tr>
<td>60</td>
<td>80.7</td>
<td>96.0</td>
<td>91.9</td>
<td>89.8</td>
</tr>
<tr>
<td>70</td>
<td>77.1</td>
<td>97.3</td>
<td>94.1</td>
<td>88.3</td>
</tr>
<tr>
<td>80</td>
<td>72.3</td>
<td>97.3</td>
<td>93.8</td>
<td>86.2</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value.

### Figure 1. Receiver operating characteristic (ROC) curves of CRP, temperature, WCC and neutrophil count in the diagnosis of infection.
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For every 1-mg/l increment in CRP, the risk of bacterial infection increased by 2.9%, and for every 1°C rise in temperature, the risk of infection increased by 3.9 times (Table 3).

**Table 3. Relationship among markers of bacterial infection and final diagnosis**

<table>
<thead>
<tr>
<th>Markers</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>1.029</td>
<td>1.019–1.039</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WCC</td>
<td>1.366</td>
<td>0.868–2.150</td>
<td>&lt;0.178</td>
</tr>
<tr>
<td>Temp (°C)</td>
<td>3.945</td>
<td>1.831–8.501</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>0.789</td>
<td>0.487–1.276</td>
<td>&lt;0.333</td>
</tr>
</tbody>
</table>

WCC, white cell count; Temp, temperature.

Discussion

It has been suggested that the CRP response to serious invasive bacterial infections may be delayed in frail older patients. This may be due to a delayed IL-6 response (a main stimulator of CRP) to infection in the old [22, 23], as well as impaired production of pro-inflammatory cytokines [24]. However, recent limited evidence on CRP behaviour in the elderly has not supported this [25, 26]. In addition, to date, most of the studies on CRP were carried out in intensive care settings [16, 27], and there is a dearth of studies on the diagnostic and therapeutic value of CRP in the elderly population [25–27]. The resolution of this issue is clinically important, as the atypical clinical symptoms and signs of infection in geriatric patients make a positive diagnosis more dependent on a rational use of supplementary tests. While procalcitonin emerges as a better test for bacterial infection [13, 16, 28], it is not readily available at our facility.

In our study, we found that patients with definite bacterial infection had higher HR and reduced diastolic blood pressure and SO2 compared with those without infection. This is congruent with previous teaching about systemic inflammatory response and cardiovascular compromise in sepsis [27]. We also found that a high serum CRP concentration in patients within 24 h of admission to hospital is predictive of bacterial infection in the elderly. This would be in keeping with general literature on CRP [16, 27, 29]. Furthermore, CRP also adds value to the assessment of a patient with suspected bacterial sepsis in the setting of elevated body temperature. On this note, elevation in body temperature was found to be highly predictive of bacterial infections. The high odd ratio associated with 1°C change reflects the substantial physiological impact of bacterial sepsis considering the narrow band of body temperatures. Conversely, in our patients, WCC and neutrophil count were not found to be predictive of bacterial infection.

Hogarth et al. [24] suggested that a cut-off value for CRP of 40 mg/l would be sufficient in elderly patients with bacterial infection, whereas another study by Sierra et al. [30] recommended that the cut-off value for sepsis should be 80 mg/l irrespective of the age of the patient [24, 30]. In our study, we found that CRP cut-off values from 30 to 60 mg/l had a good sensitivity for diagnosing bacterial infection in the elderly; however, a CRP level of 60 mg/l had the best combination of sensitivity, specificity, and positive and negative predictive values. This CRP cut-off level is lower than in the previous publication [30]. In our study of 149 patients without infection, only four patients had a strong inflammatory response associated with high CRP level. These included two cases of acute gout, one with vertebral compression fracture and the other with viral gastroenteritis (with a combined mean CRP of 191.2 ± 35.6 mg/l). This suggests that CRP elevation is not common in older patients without infection. Another reason is that setting the CRP cut-off level at higher values than 60 mg/l significantly reduces the pick-up rate of positive cases of bacterial infection which may lead to adverse clinical outcomes particularly in this group of frail older patients. Nevertheless, the CRP test should be used as an adjunct to the clinical diagnosis of infection and should never replace a clinician’s assessment.

Our data confirmed the previous literature finding that bacterial infection is a common indication for admission in elderly patients [26]. In our case, 35.7% of the admissions were diagnosed with possible, probable and definite bacterial infections. The proportion of patients admitted with cardiac diseases, respiratory disorders, and falls and fractures were also in keeping with that mentioned in the previous literature [28].

Limitations

Although this study highlighted CRP as a valuable tool in the diagnosis of bacterial infection in the elderly, we lacked information on the duration of patients’ symptoms prior to presentation. A single serum CRP collected within 24 h of admission may not reflect the true clinical course of a patient’s illness. For example, in the very early stage of bacterial infection, the CRP level may still be within the normal biochemical range as the CRP half-life is 18.8±3.9 h [31]. Anecdotally, in our experience, in a small subgroup of elderly patients with bacterial infection, the initial CRP levels were low but subsequently rose to high levels after 1 or 2 days. This would then explain the large standard deviations from the mean CRP in our patient groups (notwithstanding the other physiological attributes of CRP)—as patients might have presented in different stages of their sepsis. Another limitation of our study is that knowing the CRP values might have influenced the diagnosis of bacterial infection by the treating Aged Care teams, thus introducing a potential diagnostic bias. However, the treating teams were not involved in the study, thus limiting the direct bias on study outcomes.

Conclusion

CRP elevation in older patients within 24 h of hospitalisation is predictive of bacterial infection within clinical context.
CRP is a fast, convenient and readily available test that can be used as part of screening investigations for bacterial infection in older patients. It may guide clinicians in prompt implementation of antibiotics for bacterial infection and antibiotic avoidance in cases of non-infection. We believe that this paper adds further evidence to the usefulness of CRP in the diagnosis of bacterial infection in the older patient particularly in relation to early recognition of bacterial sepsis. Furthermore, we hope that the study will strengthen the case to implement CRP as a guide to further investigations in unwell, older patients presenting with non-specific clinical complaints.

**Key points**

- This prospective cohort study shows that a single measurement of CRP is useful in predicting bacterial infection in older person.
- At a CRP level of 60 mg/l, CRP has the best combination of sensitivity and specificity of diagnosing bacterial infection that are high.
- CRP is a fast, convenient and readily available test that can be used as part of screening investigations for bacterial infection.

**Acknowledgements**

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**Conflicts of interest**

The authors have reported no conflicts of interest. The study was supported by Bankstown–Lidcombe Hospital Specialist Trust Fund.

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The association between graded physical activity in postmenopausal British women, and the prevalence and incidence of hip and wrist fractures

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Abstract

Background: physical activity is promoted for older women as a means of maintaining health and avoiding falls and fractures. Findings relating physical activity of older women to risk of falls and fracture are contradictory. The association between level of physical activity and prevalent and incident hip and wrist fractures was examined in a large representative sample of postmenopausal British women.

Methods: data from the British Women’s Heart and Health Study, a cohort study of 4286 postmenopausal women aged 60-79, from 23 UK towns were used. Information on physical activity, anthropometry, falls and hip and wrist fractures from baseline examination and questionnaire (1999–2001) and follow-up questionnaire (2007) were available. Cross-sectional baseline prevalence data were analysed using logistic regression and cohort incidence data using a Cox proportional hazards model examining the association of physical activity with fracture outcomes.

Results: 3003 (70%) women, with complete baseline data, were studied. 13.6% had previously fractured a wrist and 1.3% a hip. Analyses unadjusted for confounders showed moderate protective associations between activity and fracture risk. After adjustment for confounders there was a weak trend towards fewer hip fractures (adjusted OR 0.13 [0.01, 1.18]) and more wrist fractures (adjusted OR 1.35 [0.76, 2.48]), amongst most active compared with inactive women. The crude incidence rate of wrist and/or hip fracture was 7.0 [5.9, 8.2] per 1000 person-years. No evidence was found for an association between physical activity and combined incident hip and/or wrist fracture (adjusted rate ratio inactive versus most active 1.69 [0.67, 4.24]).