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Abstract

Background: C-reactive protein (CRP) is a biomarker widely used for disease severity assessment and treatment of inflammatory conditions. Point-of-care testing (POCT) devices should ideally be rapid and provide similar results to standard tests done in laboratories.

Methods: 2922 serum samples were obtained from adult patients presenting to primary care with symptoms of lower respiratory infection in a European diagnostic study. The analytic performance of the CRP QuikRead POCT device (Orion Diagnostica) was evaluated by comparing results with a central laboratory method (Dimension Vista, Siemens), with both tests performed in a laboratory setting.

Results: For a CRP cut-off concentration of ≥ 30 mg/L, the QuikRead test had a sensitivity of 92.2%, and specificity of 99.4%. The mean difference between QuikRead and the central lab test was 0.4 mg/L. The slope of the Passing-Bablok regression was 0.94 (95% CI 0.93-0.95) indicating an underestimation of CRP levels of 6% by QuikRead.

Conclusions: CRP estimates obtained from the QuikRead test correlate well with a central laboratory assay and the measurement displays low inter-assay variation. Therefore, the QuikRead test is a good candidate for CRP testing in primary care.

Keywords: C-reactive protein; point-of-care test; rapid test; bedside test; respiratory infection

Introduction

C-reactive protein (CRP) is the first described acute-phase protein and is now a universal biomarker and early indicator of infectious or inflammatory conditions, related to diversified diseases, disorders and pathological conditions [1]. Measurement of CRP levels in blood are routinely performed in central hospital laboratories and many automated methods are available. However, near-patient or point-of-care testing (POCT) to measure CRP levels may be helpful in diagnosis and early management, for example to avoid unnecessary hospital referrals for acutely ill children [2] and to guide antibiotic treatment for lower respiratory tract infections [3,4]. Several POCT CRP test platforms have been developed in recent years with the advantage of providing a result within minutes. In order for these devices to be used in daily practice they should provide results comparable to laboratory based platforms for a wide variety of patients with varying CRP levels, and indications.

In a European diagnostic study on lower respiratory tract infections in primary care, we have previously demonstrated the added value of CRP levels in predicting pneumonia [5] which can be useful to start appropriate treatment and advice and avoid unnecessary use of antibiotics. In the current study we evaluate the analytical performance of a POCT device (QuikRead, Orion Diagnostica) for CRP measurement in serum samples of the above mentioned trial by comparing results with those obtained of our central laboratory method (Dimension Vista, Siemens), with assays on both platforms done in a laboratory.

Materials and methods

Serum samples from adults (≥ 18 years of age) with symptoms of lower respiratory tract infection (acute cough, ≤ 28 days) who presented to primary care were obtained in a prospective observational study as part of GRACE-09 (Genomics to Combat Resistance

against Antibiotics in Community-Acquired Lower Respiratory Tract Infection in Europe; www.grace-lrti.org) which was conducted from October 2007 to April 2010. A total of 3104 patients were included at 16 primary care networks in 12 European countries. The mean age of patients was 49.8 years (range 18 – 92 years), 40% were male and 4.5% were diagnosed with pneumonia [5,6]. Six percent of blood test data were lacking which resulted in 2922 remaining individual patient results. Venous blood was drawn at the primary care facility, serum was prepared at local laboratories and stored at -70°C. After transport to the central laboratory of the University Hospital of Antwerp, serum samples were analyzed in batch by both the central laboratory test and the POCT method on the same sample.

Dimension Vista® (Siemens) was the central laboratory platform used. This is a high-throughput analyzer using conventional particle enhanced nephelometry to determine CRP levels. The lower limit of detection of this method is 2.9 mg/L. The upper limit of detection is 290.0 mg/L. If this limit is exceeded, samples are diluted 2-fold and reanalyzed. The results are evaluated by comparison to a low-level (CRP range: 4.4 – 7.0 mg/L) and high-level (CRP range: 40.7 – 54.8 mg/L) standard (Liquichek Immunology Control, Bio-Rad).

The QuikRead 101 (Orion Corporation, Orion Diagnostica, Espoo, Finland) is a POCT or bedside immunoturbidimetric assay based on micro particles coated with anti-human CRP. It requires 20 µL of whole blood, plasma or serum and has an analytical measurement range of 8-160 mg/L. Values exceeding the upper detection limit are diluted and reanalyzed. A one-level CRP control (CRP range: 42-62 mg/L) was analyzed on every analysis day.

Analyses were all performed by trained lab technicians who were blinded to the results of the reference test and vice versa. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) were calculated by comparing the measurements obtained by the POCT CRP with the results from the central laboratory CRP. The following CRP cut-off values were used:

10 mg/L as the universally applied cut-off value to indicate production of CRP, 30 mg/L previously shown to add most diagnostic value to a "symptoms and signs" model to predict pneumonia [5] or the presence of bacterial pathogens in the airways [7] and 100 mg/L which is a critical level indicating severe infection and justifying antibiotic prescription [8].

Considering only samples with numeric values (excluding <2.9 mg/l and <8 mg/L for the central lab and POCT test, respectively), the agreement of measurements between both methods was evaluated using Passing-Bablok regression analysis, Bland-Altman plot and Spearman for the correlation coefficient. Criteria for acceptable correlation were defined as follows: the 95% confidence interval (CI) of the slope includes 1.0, the 95% CI of the intercept includes 0.0 and the correlation coefficient > 0.95. Statistical analyses were performed with MedCalc Statistical Software version 17.5.5 (MedCalc Software bvba, Ostend, Belgium).

Results

The inter-assay variation of both the POCT and central lab CRP test was determined. With the QuikRead test, a variation of 3.4% was obtained, while variations of 5.9% (low level) and 5.2% (high level) were observed for the central lab test.

Considering positive CRP concentrations to be ≥ 10 mg/L, the CRP bedside test has a sensitivity of 75.5% and a specificity of 98.8% when compared with the central lab CRP test (Table 1). However, considering CRP concentrations ≥ 30 mg/L, the sensitivity of the CRP bedside test increases to 92.2% and the specificity to 99.4% when compared with the central laboratory CRP test, with a PPV of 96.5 % and an NPV of 98.6% (Table 2).The performance of the QuikRead test increases even further at a CRP cut-off level of ≥ 100 mg/l (sensitivity = 92.6% and specificity = 99.8%) (Table 3).

The median and mean CRP values as well as the CRP range obtained using the QuikRead POCT CRP assay on the 834 serum samples with CRP concentration ≥ 10 mg/L are similar to CRP levels measured by the central laboratory assay: 32 mg/l, 50 mg/L (SD 51.2 mg/L) and 12 – 393 mg/L respectively for the QuikRead assay and 32.5 mg/L, 49.6 mg/L (SD 48.2 mg/L) and 10.1 – 392.1 mg/L for the central laboratory method.

Taking into account only the samples with a numeric value (excluding <2.9 mg/L samples for the central lab test and <8 mg/L samples for the QuikRead test) for the correlation analysis, 854 values remained. Passing-Bablok regression analysis shows a small constant bias (indicated by the intercept of 1.5) and a proportional bias (indicated by the slope of the regression line of 0.94) indicating that the QuikRead underestimates the CRP values with 6% compared to those of the central lab analysis (Fig. 1). The Spearman correlation coefficient is 0.976 but a significant deviation from linearity was shown. The Bland-Altman plot shows a mean difference between both methods of 0.4 mg/L (95% limits of agreement: –18.8 to 19.5 mg/L) which is not statistically significant (Fig. 2). The plot also shows that the reliability of the POCT CRP test decreases with increased CRP values.

Discussion

In this study, the analytical performance of the commercially available POCT CRP device QuikRead was evaluated by comparing results obtained from this platform in a laboratory (and not at the point of care) to results from a central laboratory CRP analyzer. A CRP cut-off value of 30 mg/L has previously been shown to add most diagnostic value in predicting pneumonia [5] or the presence of a bacterial infection [7] in this patient population. Taking into account this CRP cut-off, QuikRead shows good sensitivity and excellent specificity. Analysis of the correlation between both methods, demonstrates both a small constant bias and a proportional

bias. The deviation at the intercept has a relatively small impact and is less relevant than the slope of the linear regression line, which deviates with 6%. An underestimation of CRP levels by the QuikRead test compared to central lab tests is in accordance with previous studies (17% compared to the Tina-quant CRP Hitachi 912, Roche, n = 59 [9]; 15% compared to Synchron®, Beckman Coulter, n = 100 [10]). However, others report good concordance (Cobas Integra, Roche, n = 231 [11]; Architect c8000, Abbott, n = 250 [12]) or even an overestimation of CRP levels (7% compared to the BN II System, Dade Behring, n = 72 [13]) by the QuikRead test. It is clear that the large sample size in our study is an asset compared to the previously published reports.

Compared to other CRP POCT devices, the QuikRead has a more complicated pre-analytical handling of samples which takes 2.5 min [10] and is not the most user friendly apparatus [14] making it more susceptible to flaws in the procedure. This could not be tested in our study performing the analyses in a laboratory setting, which we preferred due to practical issues when testing such a large number of samples, with qualified lab technicians. The robustness of the performance of the QuikRead POCT device should therefore be evaluated using results obtained from use by different clinicians and practice staff in routine primary care. Moreover, the performance of the POCT device in that setting might also be influenced by the use of capillary whole blood, a sampling method prone to variation, instead of the serum from venous blood used in our study. However, a previous study showed no difference in CRP determination in the venous and capillary blood samples using the QuikRead device [15].

All tested CRP POCT devices in the multi-device study performed well in general with correlation coefficients > 0.95 [10]. QuikRead was shown to have low within- and between-day variation (5.7% and 6.3% respectively at a CRP concentration of 100 mg/L) compared to the other analyzers [14]. In our hands, the between-day variation was even lower, most probably due to the execution by trained lab technicians which does not reflect the real POCT

environment. Furthermore, a rather short total analysis time (without pre-analytical time) of 2 min [10] to 3 min 20 sec [14] was described. Another advantage of the POCT device, besides the rapid availability of the result, is the requirement of only small volumes of blood which can be very advantageous for use in small children, a patient group not studied here.

POCT CRP use in primary care may increase even further in the future as obtaining chest radiographs in all patients is not feasible. However, there is ongoing debate about the clinical utility of CRP POCTs. Severe pneumonias are likely to be evident clinically, so the value of POCT CRP tests should be where there is more doubt, in helping clinicians diagnose milder pneumonias – which are more difficult to detect clinically. There should also be caution about the potential for the inappropriate and inefficient use of CRP as it is introduced in practice [16], given wider concerns about the danger of 'medicalising' largely self-limiting illness. CRP test results should also always be interpreted together with clinical findings, as it was shown previously that CRP levels can be low in people with pneumonia [5].

To the best of our knowledge, this is the first study evaluating the analytical performance of the QuikRead POCT CRP test in this high number of patients with symptoms of respiratory tract infection. The data presented here are part of a large multicenter observational study and indicate the feasibility of the QuikRead POCT CRP test in primary care. However, large prospective trials in primary care or at the point of care are needed to determine the effect of CRP POCT on clinical decision-making.

Compliance with ethical standards

Funding The study was part of the European Union FP6 funded Network of Excellence GRACE. Orion Diagnostics provided the QuikRead instruments and kits for this study. The

study sponsors played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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Table legends

Table 1: Number of serum samples found positive by the QuikRead CRP assay or the central lab assay using a cut-off of ≥ 10 mg/L (n = 2922)

Table 2: Number of serum samples found positive by the QuikRead CRP assay or the central lab assay using a cut-off of ≥ 30 mg/L [5,7] (n = 2922)

Table 3: Number of serum samples found positive by the QuikRead CRP assay or the central lab assay using a cut-off of ≥ 100 mg/L (n = 2922)

Figure legends

Fig. 1: Comparison of QuikRead CRP test with central laboratory CRP values using Passing-Bablok regression analysis (n = 854).

Fig. 2: Comparison of QuikRead CRP test with central laboratory CRP values using the Bland-Altman plot (n = 854). Mean differences ± 1.96 SD for the difference are given.

Table 1: Number of serum samples found positive by the QuikRead CRP assay or the central lab assay using a cut-off of ≥ 10 mg/L (n = 2922)

		CRP central lab		TOTAL
		< 10 mg/L	≥ 10 mg/L	
CRP QuikRead	< 10 mg/L	1797	270	2067
	≥ 10 mg/L	21	834	855
TOTAL		1818	1104	2922

Table 2: Number of serum samples found positive by the QuikRead CRP assay or the central lab assay using a cut-off of ≥ 30 mg/L [5,7] (n = 2922)

		CRP central lab		TOTAL
		< 30 mg/L	≥ 30 mg/L	
CRP QuikRead	< 30 mg/L	2457	35	2492
	≥ 30 mg/L	15	415	430
TOTAL		2472	450	2922

Table 3: : Number of serum samples found positive by the QuikRead CRP assay or the central lab assay using a cut-off of ≥ 100 mg/L (n = 2922)

		CRP central lab		TOTAL
		< 100 mg/L	≥ 100 mg/L	
CRP QuikRead	< 100 mg/L	2822	7	2829
	≥ 100 mg/L	5	88	93
TOTAL		2827	95	2922

Figure 1: Comparison of QuikRead CRP test with central laboratory CRP values using Passing-Bablok regression analysis (n = 854)

Variable X	CRP_Central_lab
Variable Y	CRP_QuikRead
Sample size	854

Regression Equation

y = 1.513640 + 0.943102 x

Systematic differences	
Intercept A	1.5136
95% CI	1.1141 to 1.8700
Proportional differences	
Slope B	0.9431
95% CI	0.9319 to 0.9544
Random differences	
Residual Standard Deviation (RSD)	7.8369
± 1.96 RSD Interval	-15.3603 to 15.3603
Linear model validity	
Cusum test for linearity	Significant deviation from linearity (P<0.01)

Spearman rank correlation coefficient

Correlation coefficient	0.976
Significance level	P<0.0001
95% CI	0.973 to 0.979

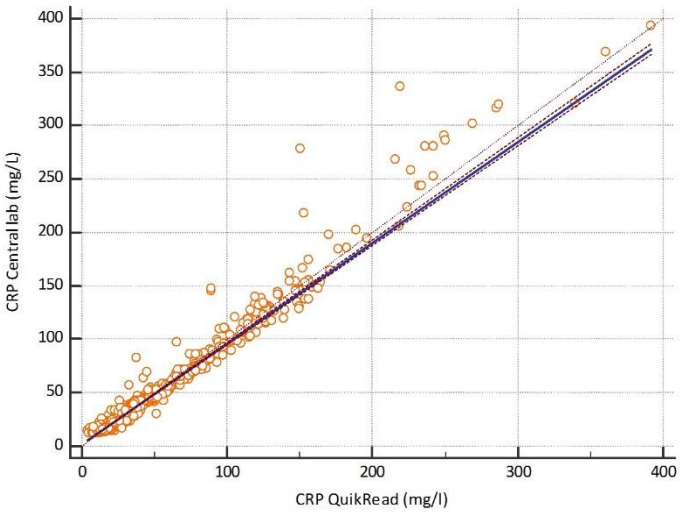

Figure 2: Comparison of QuikRead CRP test with central laboratory CRP values using the Bland-Altman plot (n = 854). Mean differences ± 1.96 SD for the difference are given