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A multicenter evaluation of a point of care CRP Test

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ABSTRACT

Background: Point-of-care (POC) C-reactive protein (CRP) testing in the primary healthcare setting is a cost-effective approach for reducing antibiotic prescriptions, but has yet to be widely adopted.

Methods: Analytical performance of the cobas CRP Test on the cobas b 101 system was evaluated at three POC sites and one reference laboratory. Within-run (repeatability), within-laboratory (intermediate precision), and between-laboratory precision (reproducibility) were assessed. Method comparison (reference test: CRP NX reagent [cobas c 501 module]) and matrix/lot-to-lot comparison experiments were conducted using prospectively collected blood samples from 217 adults (apparently healthy or with clinically relevant conditions). Usability and reliability were assessed by questionnaire and error reporting.

Results: Coefficients of variation (CV) for repeatability and intermediate precision ranged from 1.7%–4.0% and 1.9%–5.9%, respectively, for human serum pools containing CRP 4.7–350.7 mg/L; repeatability in clinical samples ranged from 1.6%–5.9% (3.3–360.3 mg/L). CVs for reproducibility ranged from 2.5%–4.0% (4.7–344.3 mg/L). CRP concentrations were comparable for capillary whole blood, serum, Li-heparin whole blood/plasma, K2 and K3 EDTA whole blood/plasma (Pearson’s \( r \geq 0.996 \)), and among three CRP Test lots (\( r \geq 0.993 \)). Clinically relevant CRP concentrations measured with the CRP Test showed good agreement with those measured by CRP NX reagent (serum, weighted Deming regression \( y = 0.97x + 0.11 \); Pearson’s \( r \geq 0.996 \)). The overall mean usability score was 4.18/5 and the error rate across 9378 tests was 1.00%.

Conclusions: The cobas CRP Test on the cobas b 101 system demonstrates robust analytic performance when used by healthcare professionals in the POC setting.

1. Introduction

C-reactive protein (CRP) is a key mediator of the acute-phase response, with blood levels of CRP increasing rapidly after an inflammatory stimulus [1–3]. Therefore, changes in serum levels of CRP are a clinically useful marker of infection, inflammation, and tissue injury [4]. CRP testing in the primary setting (i.e. point-of-care [POC]) can help reduce diagnostic uncertainty by differentiating between bacterial and viral infections [5–7] and has been shown to be cost-effective for reducing inappropriate antibiotic prescriptions [8–12].

UK National Institute for Health and Care Excellence (NICE) guidelines recommend consideration of POC CRP testing for people presenting with symptoms of lower respiratory tract infection in primary care, if pneumonia has not been diagnosed and it is unclear whether antibiotics should be prescribed [13]. Results of the CRP test can be used to guide antibiotic prescribing in people without a clinical diagnosis of pneumonia [13]. However, despite the availability of POC devices, POC CRP testing has not yet been widely adopted in primary care clinics [13–16].

The cobas b 101 POC system (Roche Diagnostics International Ltd., Rotkreuz, Switzerland) provides glycated hemoglobin (HbA\textsubscript{1c}) and lipid panel tests (measurement of cholesterol, triglyceride, and high-density lipoprotein; calculation of low-density lipoprotein) for managing diabetes and dyslipidemia at point-of-need. The test options on the cobas b
101 system have recently been expanded to include POC testing for CRP. We evaluated the analytical performance, usability and reliability of the cobas POC CRP Test (Roche Diagnostics International Ltd., Rotkreuz, Switzerland) and conducted a method comparison versus a reference comparator.

2. Methods

2.1. Study design

A multicenter evaluation of the cobas POC CRP Test was performed at three hospitals (Hospital Sant Pau, Barcelona, Spain; Catharina Ziekenhuis, Eindhoven, The Netherlands; St Antonius Ziekenhuis, Nieuwegein, The Netherlands), and one reference laboratory in Japan between May and November 2017. Each healthcare professional (nurses and physicians with limited POC device experience and no technical laboratory background) received a short training on how to obtain the sample, use the disk, and operate the device. A total of three CRP Test lots and three CRP Control lots were evaluated; each site was assigned two POC CRP Test lots and two CRP Control lots.

Within-run precision (repeatability), within-laboratory precision (intermediate precision), and between-laboratory precision (reproducibility) were assessed using six human serum pools (HSPs; Biomex GmbH [D-Heidelberg] and Kentucky Clinical Trials Laboratory [Louisville, USA]); HSP 1, <5 mg/L [healthy]; HSP 2, ~10 mg/L [cutoff]; HSP 3, ~40 mg/L [decision]; HSP 4, ~100 mg/L [acute]; HSP 5, ~280 mg/L [acute high]; HSP 6, spiked with recombinant CRP to ~350 mg/L [acute high]) and two cobas CRP Control pools (level 1, representing a low-range sample; level 2, representing a high-range sample). Method comparison, matrix comparison, lot-to-lot comparison experiments, and an additional assessment of repeatability were performed using samples collected prospectively from adults aged ≥18 years who were either apparently healthy or who had clinically relevant conditions including inflammatory disorder and associated diseases (e.g. Crohn's disease, acute asthma without infection), infection (e.g. strong evidence of infection in the clinical record, sepsis) or tissue injury (e.g. contusion, fracture, open wound, surgery). Exclusion criteria were pregnancy or breastfeeding, and any individual whom the attending clinician deemed to be clinically unstable or whose condition could be compromised by blood draw. Participants at each POC site provided two capillary blood samples (one per lot tested) and a venous whole-blood sample for measurement of serum CRP; samples were not treated with an anticoagulant. Participants enrolled at POC site 1 provided additional venous whole-blood samples for measurement of CRP in EDTA (K2 and K3) and lithium (Li)-heparin whole-blood/plasma. Samples were processed and tested immediately at each site; serum samples were split into three 1.5 mL aliquots, frozen at −70°C or colder, and shipped on dry ice for method comparison experiments performed at the reference laboratory.

The study protocol was approved by the relevant Institutional Review Board/Independent Ethics Committee at each study site prior to study initiation and the study was conducted in accordance with the Declaration of Helsinki [17]. Written informed consent was provided by all participants. The study was sponsored by Roche Diagnostics International Ltd.

2.2. Point-of-care CRP Test

The cobas POC CRP Test is an in vitro diagnostic test for the quantitative determination of CRP in human capillary whole blood and serum, and EDTA (K2/K3) and Li-heparin anticoagulated whole blood and plasma. The capillary whole-blood, serum or plasma sample is applied to the disk, which is inserted into the cobas b 101 instrument. Once the system is initiated, the liquid component of the sample is separated by centrifugation (i.e. separation from the blood cells), the isolated plasma or serum is diluted with dilution buffer, and CRP present in the sample binds with the CRP antibody–latex conjugate. The concentration of CRP is determined by photometric measurement of the latex agglutination reaction using wavelengths of 525 and 625 nm. Blood flow within the CRP test is illustrated in Supplementary Fig. 1. All experiments with the POC CRP Test in the present study were performed according to the manufacturer’s instructions.

2.3. Precision in clinical samples, whole-blood and plasma samples

Repeatability of the POC CRP Test was evaluated at a single site using EDTA K3 whole-blood and plasma samples. For each of the three reagent lots, one sample from each of the following CRP concentration categories was tested: healthy (<5 mg/L); cutoff (~10 mg/L); decision (~40 mg/L); acute (~100 mg/L); acute high (~350 mg/L). For each sample, a series of 21 sequential measurements was performed to assess within-run precision.

2.4. Precision according to CLSI EP05-A3 guidelines

Repeatability and intermediate precision of the POC CRP Test were also assessed according to Clinical and Laboratory Institute (CLSI) EP05-A3 guidelines [18]. Samples comprised six HSPs and two CRP Controls (levels 1 and 2). For each lot (n = 2 lots per site), samples were measured four times daily for 21 days (two replicates of each sample for each of two runs per day). Samples were analyzed in random order per day for 21 days.

Reproducibility of the POC CRP Test was assessed at three sites over 5 days using HSPs 1–6 and CRP Controls (levels 1 and 2). Five replicates of each sample were analyzed per day over 5 days.

2.5. Sample matrix comparison

Test performance in different matrices was compared using matched serum and capillary blood samples, and matched serum and whole-blood/plasma samples containing EDTA K2, EDTA K3, and Li-heparin as anticoagulants. Matched pairs were analyzed in parallel, in a single run for each of two POC CRP Test lots, at a single site.

2.6. Lot-to-lot comparison

POC CRP Test lot-to-lot comparison was performed using capillary whole-blood/serum samples (at three sites with a total of three disk lots) or EDTA K2, EDTA K3, and Li-heparin whole-blood/plasma samples (at a single site with two disk lots). Samples were tested in a single run per reagent lot. Multiple samples were taken from the same subject and run in parallel on two different instruments, using a different disc lot for each sample.

2.7. Method comparison

Healthcare professionals determined CRP concentrations in capillary whole blood/serum and EDTA K2, EDTA K3, and Li-heparin in whole blood/plasma using the cobas POC CRP Test (cobas b 101 system; three sites); some users had limited experience of using the system previously, and some were naïve to the system. For comparison, CRP values from matched serum samples were obtained by laboratory professionals using the cobas c 501 module (Roche Diagnostics International Ltd., Rotkreuz, Switzerland) with the CRP NX reagent (reference test; Denka Seiken, Tokyo, Japan). The reference test has a measuring range of 0.1–320 mg/L and a limit of detection of 0.05 mg/L; the CV for within-run precision ranged from 0.62–0.93% across the control samples. No interference of the test is shown with ascorbic acid up to concentration of 50 mg/dL; hemoglobin up to 500 mg/dL; bilirubin up to 30 mg/dL and intralipid up to 5 mg/dL.
3.2. Precision in clinical samples, whole-blood and plasma samples

Repeatability results for EDTA K3 whole-blood samples (mean CRP concentration 3.3–360.3 mg/L) and plasma samples (3.3–356.5 mg/L) are presented in Supplemental Table 2. Across sample types, CVs for repeatability ranged from 1.6% to 5.9%.

3.2.1. Samples

A total of 217 adult patients were recruited from semi-intensive care, cardiovascular care, ambulatory care or the emergency department, and comprised 158 males (72.8%) and 59 females (27.2%). Median age (range) was 68 (range, 22–88) years. Participants with valid measurements (n = 201) were categorized according to clinical relevance for CRP, as follows: tissue injury (n = 116 [57.7%]), infection (n = 54 [26.9%]), inflammatory disorders and associated diseases (n = 28 [13.9%]) or CRP ≤ 5 mg/L (n = 3 [1.5%]). Samples (n = 201) were categorized by CRP concentration range (Supplemental Table 1).

3.2.2. Precision according to CLSI EP05-A3 guidelines

Repeatability and intermediate precision are presented in Table 1 (overall) and Supplemental Table 3 (by lot and site) and were consistent across lots and sites. CVs for repeatability in HSPs ranged from 1.7% to 4.0% (site 1, 2.0%–4.0% [mean CRP range, 4.8–350.7 mg/L]; site 2, 1.7%–3.6% [mean CRP range, 4.7–344.2 mg/L]; site 3, 1.7%–3.9% [mean CRP range, 4.7–345.3 mg/L]; CVs for intermediate precision in HSPs ranged from 1.9% to 4.5% (site 1, 2.1%–4.1%; site 2, 1.9%–4.5%; site 3, 2.3%–4.2%).

The SD for reproducibility was 0.2 mg/L for the low-concentration HSP 1 sample (mean CRP concentration 4.7 mg/L). CVs for reproducibility ranged from 2.5% to 4.0% for HSPs 2–6 (mean CRP concentrations 10.4–344.3 mg/L; Table 2).

3.4. Matrix comparison

CRP concentrations measured using the different sample types correlated well with CRP concentrations measured in serum (Pearson’s r ≥ 0.996, intercept ≤ 0.32, slope ≥ 0.96; Supplemental Table 4); across lots and matrices, mean bias was low, ranging from 0.02% to 0.34% for low concentration samples (0–5 mg/L), from −2.18% to 0.90% for mid-range samples (5–200 mg/L), and from −5.53% to −0.74% for higher-concentration samples (Supplemental Table 5).

There was good agreement for CRP concentrations measured in serum with Li-heparin whole-blood samples (Pearson’s r, 0.998; Fig. 1A) and EDTA K3 whole blood (Pearson’s r, 0.998; Fig. 1B).

3.5. Lot-to-lot comparison

Correlations among different test lots were very good for whole-blood, plasma, and serum samples, with all Pearson’s r values ≥ 0.993, intercepts ≤ 0.30, and slopes ≥ 0.96 (Fig. 2; Supplemental Table 6). Mean bias with different lots was ≤ 2.37%.

3.6. Method comparison

There was very good correlation between CRP values measured with the cobas POC CRP Test on the cobas b 101 POC system (all sample matrices) and values measured in matched serum samples with the CRPNX test on the cobas c 501 laboratory module (Pearson’s r ≥ 0.994, slope ≥ 0.93, intercept ≤ 0.47; Supplemental Table 7). Across matrix types, lots, and sites, bias at the lower (5.0 mg/L) and upper (10.0 mg/L) medical decision points was ≤ 0.67%; results for capillary whole-blood and serum samples pooled by site and for anticoagulated whole-blood and plasma samples at a single site are presented in Table 3. Biases for the comparison of the POC CRP Test versus the CRPNX test (serum) are presented in Table 3. For the CRP range 3–200 mg/L, mean bias (95% CI) was −2.05% (−10.54, 6.43) for serum and −2.05% (−15.64, 11.54) for capillary whole blood. Example Bland Altman plots are shown for serum in Fig. 3A and capillary whole blood in Fig. 3B. When CRP was measured in serum samples with the POC CRP Test and CRPNX (pooled site; lot 1; n = 130 samples), weighted Deming regression analysis yielded a Pearson’s r of 0.996 (Supplemental Fig. 2A). Weighted Deming regression analysis of the POC CRP Test
(whole capillary blood; lot 1) versus CRP NX test (serum) results, based on pooled site data for 136 samples, yielded a Pearson’s r of 0.994 (Supplemental Fig. 2B).

3.7. Operator-reported usability

Overall mean score for operator-reported usability assessed across six domains was 4.18 out of 5 (i.e. between “good” and “excellent”; n = 7 completed questionnaires across the three sites). Mean scores by individual domain are presented in Supplemental Fig. 3. Of interest, all sites noted the rapid turnaround time for results and the ease of use of the instrument, but also the missing battery-operated modus, meaning that it was cumbersome to plug in the instruments at patient beds.

A total of 9378 POC CRP Test disks were tested during this performance evaluation and 94 errors were reported (~1% error rate). Most errors (46%) were reaction errors due to overfilling the disk where the sample is able to move out of the chamber due to backflow. The second most common error (24%) was large or insufficient sample, and most cases occurred with serum or control solution (only one error was reported with capillary whole blood). None of the reported errors were associated with wrong measurement results.

4. Discussion

Use of CRP testing at POC can help to reduce inappropriate anti-biotic prescriptions [8–12]; however, widespread use in primary care settings has not yet materialized. Availability of easy-to-use and reliable CRP testing may facilitate greater use by clinicians. In the current analyses, we show that the cobas POC CRP Test delivered precise and repeatable CRP values with clinical specimens (including samples with very high CRP values) and with HSPs measured according to CLSI EP05-A3 criteria. Notably, CVs for imprecision were well below the specifications reported in the desirable biological variation database, which state a CV for imprecision of 21.1% [19]. CRP values measured using different sample types correlated well, with low mean bias. Correlations between different test lots were very good, indicating that different lots of the POC CRP Test perform equally well. Moreover, CRP values measured in a range of sample types with the POC CRP Test demonstrated very good correlation with CRP values measured in serum samples with the CRP NX test on the cobas c 501 module; these results indicate that the POC CRP Test delivers comparable performance to laboratory CRP testing. Finally, usability of the cobas b 101 system was rated as “good” to “excellent” by operators, and reported error rates were low, indicating convenience of the system for use in the POC environment.

POC CRP testing offers several clinical and health-economic advantages. Compared with CRP testing, procalcitonin testing is more expensive in both POC and automated settings [20,21]. Notably, POC CRP testing has been shown to be cost-effective for reducing inappropriate antibiotic prescriptions in patients presenting with suspected respiratory tract infection [13,22]. A recent systematic review of randomized controlled trials and observational studies reported that POC CRP testing was associated with a significant 25% reduction in antibiotic prescribing at the index consultation relative to no POC CRP
testing (risk ratio 0.75; 95% confidence interval [CI], 0.67–0.83) [8]. Reductions in unnecessary antibiotic prescriptions are desirable given the growing problem of antibiotic resistance [23]. Moreover, over half of patients presenting to primary care with lower respiratory tract infections are prescribed antibiotics [24], yet there is limited evidence that the marginal benefits of these treatments outweigh the risk for harm [25,26]. Although CRP tests are available through local hospital pathology services at a lower cost, POC testing allows the findings to be discussed between patient and primary care practitioner during the consultation and may be helpful in persuading patients to agree to a non-antibiotic approach [13,27].

UK NICE guidelines recommend that POC CRP testing is considered for people presenting to primary care with symptoms of lower respiratory tract infection. The guidelines recommend that antibiotic therapy should not be routinely offered if the CRP concentration is < 20 mg/L, that a delayed antibiotic prescription (i.e. for use at a later date, if symptoms worsen) should be considered if the CRP concentration is 20–100 mg/L, and that antibiotic therapy should be offered if the CRP concentration is ≥ 100 mg/L.

Clinical experience with existing POC CRP tests supports their use in primary care [28]. For example, Matheeussen and colleagues [28] compared a CRP QuikRead POC testing device (Orion Diagnostica, Espoo, Finland) with a central laboratory method for CRP measurement in over 2900 serum samples from adult patients presenting to primary care with symptoms of lower respiratory infection. The POC device had a sensitivity of 99% and specificity of 99.4% at a CRP cutoff of ≥ 30 mg and was deemed a good candidate for POC CRP testing. Interestingly, the slope of the Passing–Bablok analysis suggested a 6% underestimation of CRP

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**Fig. 2.** Lot-to-lot comparison: Passing–Bablok regression analysis of CRP values measured with different lots of the POC CRP Test using serum (A and B) and capillary whole blood (C and D).

CRP, C-reactive protein; WB, whole blood.
### Table 3
Method comparison: mean bias for CRP measured with the cobas POC CRP Test (cobas b 101 POC system) using (A) capillary whole blood and serum (data from all sites combined), (B) EDTA K2/K3 and Li-heparin in whole blood and plasma samples (data from POC site 1 only), on the CRP NX (cobas c 501 laboratory module).

#### A

<table>
<thead>
<tr>
<th>Lot</th>
<th>CRP range/*MDP (mg/L)</th>
<th>Capillary whole blood</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean bias, % (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>1</td>
<td>3–200</td>
<td>121</td>
<td>−2.05 (−15.64, 11.54)</td>
</tr>
<tr>
<td></td>
<td>200–400</td>
<td>15</td>
<td>−2.41 (−16.50, 11.68)</td>
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<td>3–200</td>
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<tr>
<td></td>
<td>200–400</td>
<td>17</td>
<td>−4.43 (−11.27, 2.40)</td>
</tr>
<tr>
<td>3</td>
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<td>116</td>
<td>−3.26 (−13.06, 6.54)</td>
</tr>
<tr>
<td></td>
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<td>12</td>
<td>−6.38 (−18.63, 5.88)</td>
</tr>
</tbody>
</table>

#### B

<table>
<thead>
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<th>Lot</th>
<th>CRP range/*MDP (mg/L)</th>
<th>Whole blood</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDTA K2</td>
<td>EDTA K3</td>
<td>Li-heparin</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Mean bias, 95% CI (%)</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>200–400</td>
<td>10</td>
<td>−3.02 (−10.43, 4.40)</td>
</tr>
<tr>
<td>2</td>
<td>3–200</td>
<td>72</td>
<td>1.55 (−2.67, 5.77)</td>
</tr>
<tr>
<td></td>
<td>200–400</td>
<td>72</td>
<td>−1.02 (−2.95, 0.92)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CRP, C-reactive protein; MDP, medical decision point; PL, plasma; WB, whole blood.
levels by the POC device (Passing–Bablok slope 0.94; 95% CI, 0.93–0.95) [28]. For comparison, in the present study there was strong agreement between the POC CRP Test and the central laboratory reference test (CRPNX reagent); for serum samples, the slope of the weighted Deming regression was 0.97 and the upper 95% CI ranged from 0.98 to 0.99 across lots, indicating a 3% underestimation of CRP concentrations.

Strengths of the present study include the use of clinical samples derived from prospectively enrolled individuals, and that precision was measured according to CLSI EP05-A3 guidelines [18]. Importantly, the method comparison was performed by healthcare professionals in the POC environment and laboratory operators at a reference laboratory (i.e. relevant user groups), and used a relevant reference test (CRPNX). A reference range for CRP specific to the cobas POC CRP Test was not determined in the present study; therefore, further studies are warranted to define a reference range and explore the utility of this POC CRP Test in clinical populations. As this study was conducted in hospital settings, additional studies conducted in a primary care population would be beneficial to validate our findings and further examine the utility of the POC CRP Test in clinical populations. Use of the POC CRP Test would be expected to have equivalent benefit in clinical populations, particularly since all healthcare professionals are able to learn to use the device after a short training session.

In conclusion, these findings indicate that healthcare professionals can obtain precise and reproducible CRP values with the cobas POC CRP Test that show very good correlation with laboratory measurements. Importantly, operators considered the system convenient for use in the POC environment.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiochem.2019.06.009.

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[16] [No authors listed], Point-of-care CRP testing in the diagnosis of pneumonia in adults, Drug Ther. Bull. 54 (2016) 117–120.

