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Comparison of Two Immunoturbidimetric C-Reactive Protein Assays on the Same Automated Analyzer

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ABSTRACT

Objective: To compare the analytical performance of 2 immunoturbidimetric C-reactive protein (CRP) reagents using the same automated analyzer and to evaluate whether an alternative reagent provides clinically acceptable results.

Methods: This prospective method-comparison study used 44 residual serum samples. C-reactive protein levels were measured on a Beckman Coulter AU5800 clinical chemistry analyzer using the original Beckman Coulter reagent and an alternative Archem reagent. Method comparison was performed in accordance with CLSI EP09-A3 guidelines using percentage difference plots and Passing–Bablok regression analysis. Precision was evaluated based on CLSI EP15-A3 recommendations. Acceptable bias was defined as 23.4% according to the EFLM Biological Variation Database.

Results: The mean percentage difference between the methods was −15.4% (95% CI: −18.0 to −12.9), which was within the predefined acceptable bias limits. Passing–Bablok regression analysis showed a slope of 0.78 (95% CI: 0.73-0.81) and an intercept of 0.56 (95% CI: 0.36-0.83), indicating proportional and constant differences between the methods. Both reagents demonstrated acceptable within-run and between-run precision. Within-run precision values exceeded the manufacturer's specifications, whereas between-run precision results were consistent with the reported values.

Conclusion: Despite the presence of proportional and constant differences, the alternative CRP reagent demonstrated clinically acceptable analytical comparability within biological variation–based limits. These findings support its potential use in routine laboratory practice, provided that the same reagent is consistently used for patient follow-up.

Keywords: Analytical performance, C-reactive protein, immunoturbidimetric assay, method comparison

INTRODUCTION

C-reactive protein (CRP) is a well-established acute-phase protein synthesized predominantly by hepatocytes in response to pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor-alpha (TNF-α). Since its discovery, CRP has become one of the most widely used biomarkers in clinical practice due to its rapid and significant increase in response to inflammation, infection, tissue injury, and malignancy. Its clinical utility extends beyond acute inflammatory conditions, because CRP is also recognized as a valuable indicator in cardiovascular risk assessment and in chronic inflammatory disorders. Consequently, CRP measurement is among the most frequently requested laboratory tests worldwide.[1,2]

With increasing clinical demand, various analytical methods for CRP measurement have been developed, including immunoturbidimetric, immunonephelometric, enzyme-linked immunosorbent assay (ELISA), and high-sensitivity CRP (hs-CRP) assays. Among these, immunoturbidimetric methods are widely preferred in routine clinical laboratories due to their compatibility with automated analyzers, rapid turnaround time, and cost-effectiveness. However, despite these advantages, variability across analytical systems and reagents may affect the comparability of results.[3]

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A major challenge in CRP testing is the lack of complete standardization across different methods and platforms. Previous studies have shown that even when strong correlations are observed between assays, systematic differences may still exist, leading to clinically relevant discrepancies in reported CRP values. These inconsistencies may arise from variations in assay design, antibody specificity, calibration procedures, and analytical sensitivity, potentially resulting in misinterpretation of patient results, particularly near clinical decision thresholds.[4,5]

Numerous method comparison studies have evaluated the analytical performance and agreement of CRP assays. Most studies have focused on comparisons between different analytical principles (e.g., immunoturbidimetry versus nephelometry or ELISA) or between different analyzers.[6,7] Although these studies generally report high correlation coefficients, they also highlight the presence of bias and variability, especially at low CRP concentrations. More recent studies comparing different immunoturbidimetric reagents across multiple platforms have shown that, despite overall good agreement, minor differences between reagents can influence analytical performance.[8]

However, limited data are available on the direct comparison of different reagents using the same analytical method and the same automated platform. Such comparisons are particularly important, as they allow the evaluation of reagent-related variability while minimizing confounding factors associated with instrument and methodological differences. Furthermore, the increasing need for cost-effective laboratory practices has led to the introduction of alternative reagents, necessitating rigorous performance evaluation before their implementation in routine use.

Therefore, the aim of the present study was to compare the analytical performance of 2 different immunoturbidimetric CRP reagents using the same automated analyzer. By evaluating agreement, bias, and analytical performance characteristics, the authors sought to determine whether an alternative reagent could provide clinically acceptable results for routine laboratory use.

METHODS

Study Design

This prospective method-comparison study was conducted in the Medical Biochemistry Laboratory at KastamonuTraining and Research Hospital. The study was designed and performed in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines, specifically EP09-A3 for method comparison and bias estimation.[9] In addition, precision verification procedures were performed in accordance with the CLSI EP15-A3 recommendations,[10] and the study was reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Residual serum samples obtained from routine laboratory testing were used. All samples were anonymized prior to analysis. The minimum sample size requirement defined by CLSI EP09-A3 (≥40 patient samples) was fulfilled.[9]

Ethical approval was obtained from the Clinical Research Ethics Committee of Kastamonu University (Approval No: 2022-KAEK-138; Date: 14.12.2022). Written informed consent was waived by the Ethics Committee due to the use of anonymized residual samples obtained from routine clinical practice.

Samples and Pre-analytical Procedures

Samples were collected from patients for whom CRP testing had been requested as part of routine clinical care. Blood samples were drawn from the antecubital vein with patients in a seated position into serum separator tubes containing a clot activator and gel (Becton Dickinson, New Jersey, USA).

Only samples with sufficient residual volume (≥0.5 mL) were included. Samples with visible hemolysis, icterus, or lipemia, as well as those with insufficient volume, were excluded in accordance with reagent manufacturer recommendations.

All samples were processed and analyzed under standardized, controlled conditions, and measurements for both reagents were performed on the same day to minimize potential variability from sample storage and handling.

Analytical Methods and Reagents

C-reactive protein measurements were performed on a Beckman Coulter AU5800 (Beckman Coulter, Brea, CA, USA) automated clinical chemistry analyzer using the immunoturbidimetric method. Two different reagents were evaluated:

- Beckman Coulter CRP Latex reagent (Beckman Coulter, Brea, CA, USA; lot no. 2727; linear measuring range: 0.2-480 mg/L).[11]
- Archem Diagnostics CRP TURBI WR reagent (Archem Diagnostics, Istanbul, Türkiye; lot no. 130; linear measuring range: 2-350 mg/L).[12]

Both assays are based on latex-enhanced immunoturbidimetry, in which CRP in the sample reacts with anti-human CRP antibodies coated on latex particles, forming insoluble antigen–antibody complexes. The resulting increase in turbidity is measured photometrically and is proportional to the CRP concentration.

For both reagents, absorbance was measured at 570 nm. The Archem reagent was traceable to the Human CRP reference material (NIBSC code 85/506), whereas the Beckman Coulter reagent was calibrated against the International Federation of Clinical Chemistry (IFCC) reference material CRM 470.

Each sample was analyzed once with each reagent under identical analytical conditions.

Quality Control and Precision Verification

Prior to analysis, routine daily maintenance procedures of the analyzer were performed. Both reagents were calibrated according to the manufacturers' instructions using CRP Latex Calibrator Set (Beckman Coulter, Brea, CA, USA; lot no. 1073A) and CRP TURBI WR Calibrator Set (Archem Diagnostics, Istanbul, Türkiye; lot no. 304).

Main Points

- *Different C-reactive protein (CRP) reagents may produce biased results even when correlation is high.*
- *Evaluating bias and clinical acceptability is essential in method comparison studies.*
- *The alternative CRP reagent showed acceptable performance within biological variation limits.*
- *Within-run precision may differ from manufacturer claims under routine laboratory conditions.*
- *Consistent use of the same reagent is important for accurate patient follow-up.*

Internal quality control (IQC) was assessed using 2 levels (low and high) of control material (Beckman Coulter ITA Control Serum Level 1 and Level 2; Beckman Coulter, Clare, Ireland; lot nos. 1052B and 1053C, respectively), and acceptable analytical performance was confirmed before sample analysis.

Precision verification studies were performed to evaluate within-run (intra-day) and between-run (inter-day) reproducibility in accordance with CLSI EP15-A3 recommendations using the same control materials.[10] Within-run precision was assessed by analyzing 2 levels of control materials in 20 consecutive replicates within a single run. Between-run reproducibility was evaluated by measuring the same control levels twice daily (morning and afternoon) over 5 consecutive days.

Statistical Analysis

Method comparison analyses were performed using a web-based application developed in accordance with the CLSI EP09-A3 principles.[13] The comparative method (original reagent) was assigned as the independent variable (X), and the candidate method (alternative reagent) as the dependent variable (Y).

Agreement Between Methods Was Evaluated Using

- Difference plot analysis (percentage difference)
- Passing–Bablok regression analysis

Regression parameters (slope and intercept) and their 95% confidence intervals (CIs) were calculated.

The desirable analytical performance specification for maximum allowable bias for CRP was set at 23.4%. This threshold was derived according to Fraser's biological variation model using the within-subject (CV_I: 34.7%) and between-subject (CV_G: 87.1%) biological variation estimates reported in the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Biological Variation Database.[14]

RESULTS

A total of 44 serum samples were included in the study. The patients' ages ranged from 1 to 86 years, with a mean age of 48.4 ± 20.7 years. The study population consisted of 21 males and 23 females. The distribution of CRP concentrations across clinically relevant ranges is summarized in Table 1.

Precision Analysis

The within-run and between-run precision results for both reagents are summarized in Table 2. Both reagents demonstrated acceptable precision under routine laboratory conditions. When compared with manufacturer-reported performance data, a direct numerical comparison was limited due to differences in control material concentrations. However, the observed precision values were within a comparable range. The within-run precision values were generally higher (indicating lower precision) than those reported by the manufacturers, whereas the between-run precision results were largely consistent with the stated specifications.[11,12]

Table 1. Distribution of Serum C-Reactive Protein Concentrations Across Predefined Clinical Ranges

CRP, mg/L	2-5	5-10	10-50	>50
Sample size, n (%)	9 (20)	13 (30)	14 (32)	8 (18)

CRP, C-reactive protein.

Difference Plot and Passing–Bablok Regression Analyses

The agreement between the 2 methods was evaluated using a percentage difference plot (Figure 1). The Shapiro–Wilk test indicated that the differences were normally distributed ($P = .427$). The mean percentage difference between the candidate and comparative methods was −15.4% (95% CI: −18.0 to −12.9), which remained within the predefined acceptable bias limits (±23.4%).

Passing–Bablok regression analysis (Figure 2) yielded a slope of 0.78 (95% CI: 0.73-0.81) and an intercept of 0.56 (95% CI: 0.36-0.83), indicating proportional and constant differences between the 2 methods. Despite these differences, the regression line remained within the predefined acceptable bias limits.

DISCUSSION

In the present study, the authors compared 2 immunoturbidimetric CRP reagents using the same analytical platform. Although proportional and constant differences were observed between the methods, the overall bias remained within the predefined acceptable limits based on biological variation criteria. These findings indicate that the alternative reagent demonstrates acceptable analytical comparability for routine laboratory use.

C-reactive protein is one of the most widely used inflammatory biomarkers in clinical practice, and its measurement plays a critical role in the diagnosis, monitoring, and prognostic evaluation of various conditions, including infections, cardiovascular diseases, and chronic inflammatory disorders.[1,15] Due to this extensive clinical use, analytical accuracy and comparability between methods are of paramount importance.

In the literature, numerous studies have demonstrated that different analytical methods for CRP measurement, including immunoturbidimetry, nephelometry, ELISA, and immunofluorometric assays, may yield significantly different results despite high correlation coefficients. For instance, López-Campos et al[5] reported that although ELISA and nephelometric methods showed good correlation, significant differences in absolute CRP values were observed, highlighting the lack of assay standardization. Similarly, Maggiore et al[16] demonstrated substantial discrepancies between different automated CRP assays, emphasizing that method-dependent variability may influence clinical interpretation. In line with these findings, Üstündağ et al[17] also reported a strong correlation ($r = 0.993$) between immunofluorometric and immunoturbidimetric methods; however,

Table 2. Precision Analysis of Beckman Coulter and Archem C-Reactive Protein Reagents

	Mean (mg/L)		Within-Run Precision (CV%)		Between-Run Precision (CV%)	
Control	Beckman Coulter	Archem	Beckman Coulter	Archem	Beckman Coulter	Archem
Level 1	12.6	11.2	1.47	2.26	1.73	2.28
Level 2	23.8	25.2	0.91	2.91	1.22	3.08

CV, coefficient of variation.

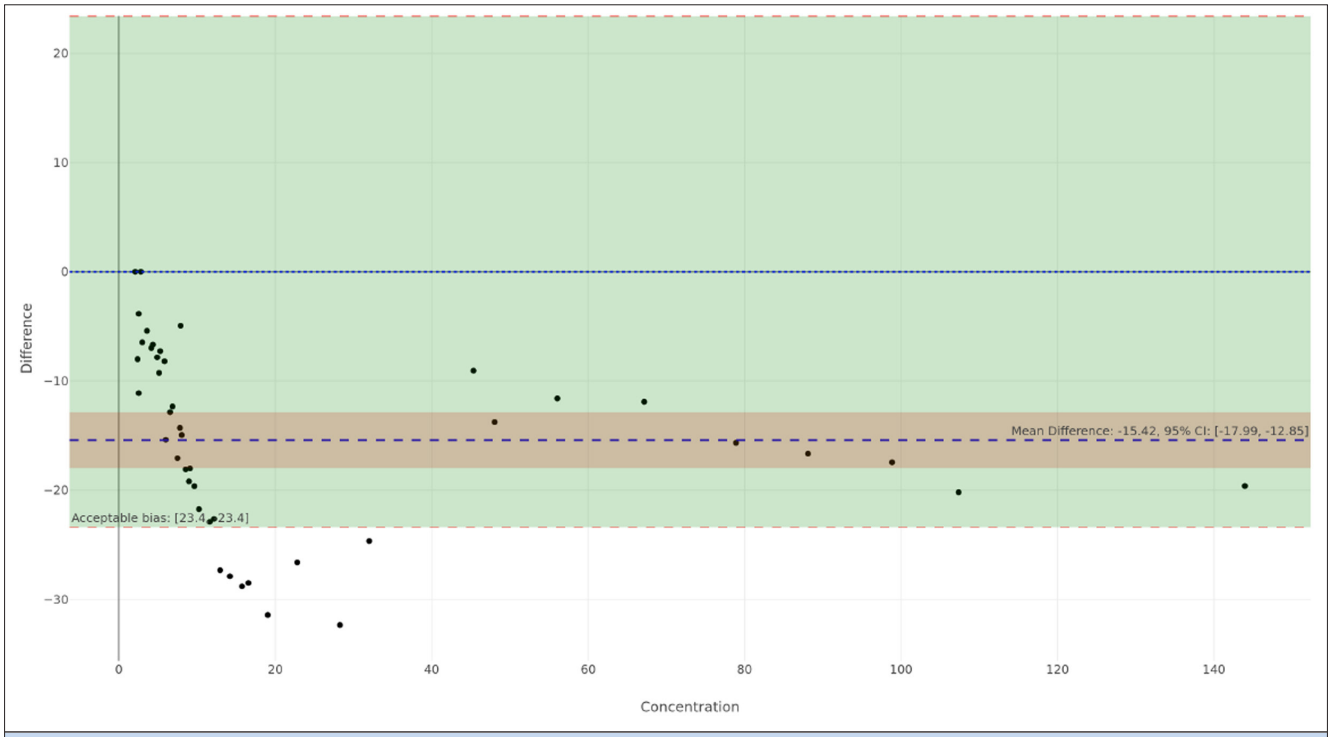

Figure 1. Percentage difference plot showing agreement between the comparative (Beckman Coulter) and candidate (Archem) C-reactive protein (CRP) methods. The mean difference was −15.4% (95% CI: −18.0 to −12.9). The shaded area represents the acceptable bias limits (±23.4%).

differences in regression characteristics indicated that high correlation does not necessarily imply full agreement between methods.

The findings are consistent with these observations, as both statistical analyses in this study revealed proportional bias. However, unlike many previous studies comparing fundamentally different analytical techniques, this study design minimized methodological variability by using the same analyzer and analytical principle. This approach allowed the authors to specifically evaluate reagent-related differences, which represent a less frequently investigated but clinically relevant source of variability.

Previous studies comparing immunoturbidimetric assays have generally reported high levels of agreement between methods.

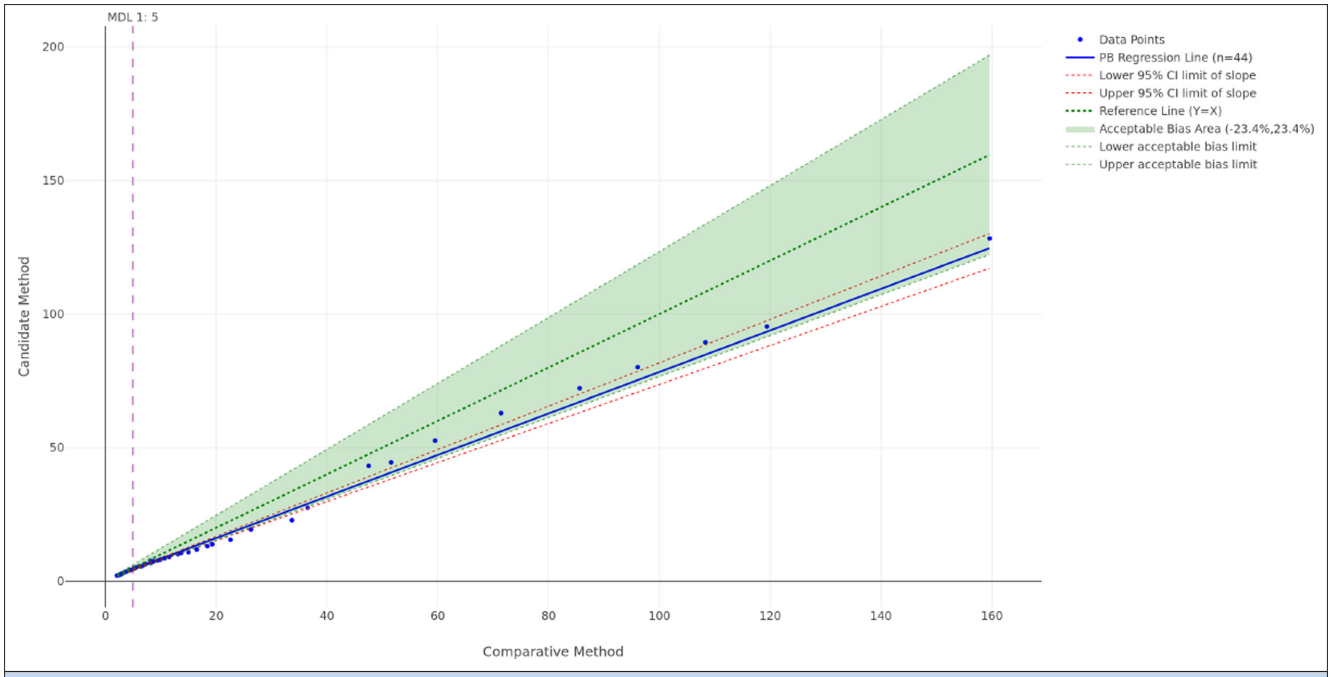

Figure 2. Passing–Bablok regression analysis comparing the candidate (Archem) and comparative (Beckman Coulter) C-reactive protein (CRP) methods. The slope was 0.78 (95% CI: 0.73-0.81) and the intercept was 0.56 (95% CI: 0.36-0.83). The shaded area indicates acceptable bias limits based on biological variation criteria.

For example, Şişman et al[6] demonstrated a strong correlation and acceptable agreement between 2 particle-enhanced immunoturbidimetric CRP assays, although variability was noted at low concentrations. Similarly, Lolekha et al[7] reported a high correlation between high-sensitivity CRP methods but observed systematic differences that affected risk classification in some cases. These findings support the concept that high correlation does not necessarily imply interchangeability between methods.

In line with these studies, the results showed that although agreement between reagents was acceptable within predefined bias limits, proportional differences were observed. This finding highlights the importance of evaluating not only correlation but also bias and clinical acceptability when comparing analytical methods. Consistent with previous studies comparing different CRP measurement systems, it has been emphasized that although multiple methods may provide acceptable results, the use of the same method for patient follow-up is essential to avoid clinically misleading differences.[18]

Nevertheless, caution is warranted when interpreting the observed agreement. C-reactive protein exhibits considerable biological variation, and the allowable bias limit of ±23.4% derived from biological variation criteria is relatively wide. Although the mean bias observed in the present study remained within this predefined limit, the Archem reagent produced results that were, on average, 15.4% lower than those obtained with the Beckman Coulter reagent. Such differences may have limited clinical impact at markedly elevated CRP concentrations but could become more relevant near clinical decision thresholds. For example, patients with CRP concentrations close to commonly used cut-off values may be classified differently depending on the reagent used. Because clinical decision-level bias analyses were not performed, the potential impact of these differences on individual patient classification could not be fully assessed and warrants further investigation. Furthermore, the Passing–Bablok regression analysis demonstrated proportional and constant differences between the 2 reagents, supporting the recommendation that the assays should not be used interchangeably during serial patient monitoring.

Another important aspect of this study is the evaluation of analytical precision. Both reagents demonstrated acceptable within- and between-run precision under routine laboratory conditions. However, the observed within-run precision values were higher (indicating worse performance) than those reported by the manufacturers, whereas the between-run precision results were within the stated specifications. These findings suggest that although both assays meet acceptable performance criteria, differences between observed and manufacturer-reported precision values may be related to variations in control material concentrations, sample matrix, and routine laboratory conditions. Comparable precision performances have been reported in previous studies evaluating immunoturbidimetric CRP assays.[19]

From a practical perspective, immunoturbidimetric methods are widely preferred in routine laboratories due to their automation, rapid turnaround time, and cost-effectiveness. Several studies have emphasized that these methods can serve as reliable alternatives to more complex or expensive techniques, particularly in high-throughput clinical settings.[20] Recent developments in latex-enhanced immunoturbidimetric assays have further improved analytical sensitivity and measurement range, with reported high accuracy and strong agreement with reference methods, supporting their widespread use in routine laboratories.[21] In addition, rapid, point-of-care CRP testing systems provide acceptable analytical performance, although variability between systems remains a concern.[19]

This study has several limitations. First, the sample size, although compliant with CLSI EP09-A3 recommendations, was relatively limited. Second, each sample was measured only once with each reagent, and replicate measurements for method comparison were not performed, which may affect the robustness of the comparison. Third, a clinical decision-level bias analysis was not performed, which could have provided additional insight into the impact of method differences on clinical interpretation. Finally, the study was conducted using a single analytical platform, and therefore, the findings may not be directly generalizable to other instruments or laboratory settings.

CONCLUSION

In conclusion, although statistically significant proportional and constant differences were observed between the 2 immunoturbidimetric CRP reagents, the overall bias remained within the predefined acceptable limits based on biological variation criteria. The use of EFLM-derived allowable bias provides a clinically meaningful framework for interpreting these analytical differences. These findings indicate that the alternative reagent demonstrates clinically acceptable analytical comparability with the original reagent when used on the same analytical platform. The results support the potential use of the alternative reagent in routine laboratory practice. Economic evaluations were beyond the scope of the present study, and future studies incorporating formal cost analyses would be valuable. Nevertheless, consistent use of the same reagent is recommended for patient follow-up to avoid misinterpretation due to method-dependent variability.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received from the Clinical Research Ethics Committee of Kastamonu University (Approval No: 2022-KAEK-138; Date: 14.12.2022).

Informed Consent: Written informed consent was waived by the Ethics Committee due to the use of anonymized residual samples obtained from routine clinical practice.

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Declaration of Interests: The author has no conflicts of interest to declare.

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