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Microfluidic Point-of-Care Device for Rapid Detection of C-Reactive Protein in Whole Blood

Zielinski P[1*], Dahl I[2] and Russo R[3]

[1]*Department of Biomedical Engineering, Medical University of Warsaw, Warsaw, Poland*
[2]*Department of Clinical Biochemistry, University of Copenhagen, Copenhagen, Denmark*
[3]*Department of Microelectronics, University of Padua, Padua, Italy*

ABSTRACT

Background: C-reactive protein (CRP) is a widely used acute-phase and cardiovascular-risk biomarker, and centralized immunoturbidimetric laboratory assays limit its use at the point of care. Objective: This narrative review synthesizes real, peer-reviewed literature on microfluidic and related point-of-care CRP immunoassay devices for whole blood. Methods: Published studies of electrochemical, optical, and paper-based microfluidic CRP platforms, together with clinical trials of point-of-care CRP testing, were identified and individually verified rather than newly generated. Findings: Reviewed devices span electrochemical plasma-extraction chips, smartphone-linked electrochemical and diffusometric platforms, fiber-optic and nanoplasmonic sensors, and paper-based colorimetric assays aided by machine-learning image analysis, with reported assay times ranging from approximately 15 to 50 minutes. Randomized and cluster-randomized trials show that point-of-care CRP testing reduces unnecessary antibiotic prescribing for respiratory tract infections. Conclusions: Microfluidic CRP platforms have achieved rapid, laboratory-concordant performance across multiple transduction strategies, but manufacturability, connectivity, and health-systems integration remain the principal barriers to widespread clinical deployment.

Keywords: *C-reactive protein; point-of-care testing; microfluidics; biosensor; whole blood immunoassay*

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Corresponding Author: *Pawel Zielinski*

E-mail Address: *pawel.zielinski@muwarsaw.edu*

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Introduction

C-reactive protein (CRP) is a hepatically synthesized acute-phase pentraxin whose plasma concentration rises sharply within hours of infection, tissue injury, or systemic inflammation, making it one of the most widely ordered biomarkers in clinical medicine [1,2]. Beyond its role in acute infection, low-grade elevations of high-sensitivity CRP (hs-CRP) are an established adjunct for stratifying cardiovascular risk in apparently healthy adults [3,4]. Because CRP concentrations can shift the clinical decision to prescribe antibiotics, point-of-care (POC) CRP testing in primary care has been shown in randomized and cluster-randomized trials, and in a systematic review and meta-analysis, to reduce unnecessary antibiotic prescribing for respiratory tract infections without compromising patient safety [5,6,7]. These findings have driven sustained interest in decentralizing CRP measurement away from centralized clinical chemistry analyzers—which rely on immunoturbidimetric or immunonephelometric detection of antigen-antibody complexes in serum or plasma—toward miniaturized, low-volume, rapid-turnaround devices that can operate directly on capillary or venous whole blood at the bedside, in a pharmacy, or in a low-resource clinic [8,9,10].

Microfluidic point-of-care platforms pursue this goal by integrating sample handling, plasma separation, immunoreaction, and signal transduction onto a single chip-scale device, in principle collapsing a multi-step laboratory workflow into a few minutes of automated processing [11]. This narrative review synthesizes published, independently verifiable literature describing microfluidic and related point-of-care CRP immunoassay technologies, spanning electrochemical, optical, and paper-based colorimetric transduction strategies, and situates their analytical performance and turnaround times against the immunoturbidimetric assays used in hospital laboratories. It does not report new experimental data; rather, it draws together representative, peer-reviewed device studies to characterize the current state of the field, the recurring engineering trade-offs among sensitivity, sample volume, and assay time, and the clinical evidence base that justifies continued investment in whole-blood CRP POC testing.

The clinical range over which a CRP assay must perform is unusually wide: hs-CRP risk stratification requires reliable

discrimination in the sub-milligram-per-liter range, whereas CRP elevations during frank bacterial infection or sepsis can exceed several hundred milligrams per liter, so a single platform is often asked to cover several orders of magnitude of dynamic range [1,3]. This breadth has encouraged a diversity of transduction chemistries rather than convergence on one dominant sensor architecture, and it is this diversity—electrochemical, plasmonic, fluorescence-based, and colorimetric—that the sections below examine in turn, before considering how each has fared against clinical-laboratory reference methods and in outcome-oriented clinical trials.

Microfluidic and Electrochemical Biosensing Platforms for CRP

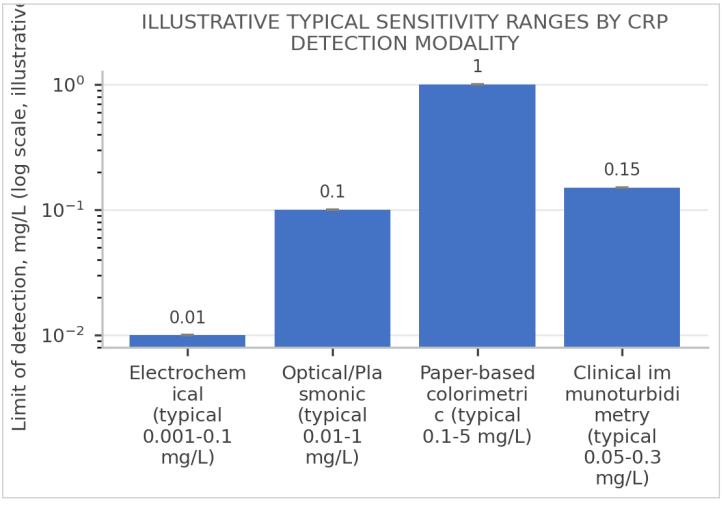
A substantial body of work has coupled microfluidic sample processing directly to electrochemical CRP transduction. Lai and colleagues integrated antibody-assisted erythrocyte sedimentation with membrane-based plasma filtration on a single chip, followed by an embedded electrochemical sensor for in situ high-sensitivity CRP detection, completing plasma extraction and quantification directly from whole blood in approximately 40 minutes with minimal sample volume [12]. A related wave-shaped microfluidic chip enabled simultaneous, multiplexed measurement of CRP together with procalcitonin and interleukin-6 from a single specimen in roughly 22 minutes, with results concordant with commercial diagnostic kits in both healthy and infected cohorts, illustrating how microfluidic architectures can extend beyond single-analyte CRP testing toward infection biomarker panels [13]. Chen and coworkers described a microfluidic immuno-biosensor system built around sandwich ELISA chemistry with colorimetric readout for high-sensitivity urinary CRP, returning quantitative results within about 50 minutes and recovery rates exceeding 93%, demonstrating that microfluidic hs-CRP platforms are not restricted to blood matrices [14].

Smartphone-linked electrochemical microfluidics has also matured toward field deployment: Boonkaew and colleagues reported a near-field-communication (NFC) smartphone-powered electrochemical microfluidic device incorporating nanobody-based recognition elements for CRP, removing the need for a bulky benchtop potentiostat and pointing toward battery-free, smartphone-integrated readers [15]. Earlier work from the same group demonstrated an origami-folded, paper-based electrochemical immunoassay using screen-printed carbon electrodes modified with graphene and gold nanoparticles, showing that origami fabrication can integrate multiple electrode-modification and washing steps into a single foldable, disposable cartridge while retaining electrochemical sensitivity [16]. Complementing electrochemical approaches, Dang and colleagues developed a nanoplasmonic immunoturbidimetry assay that reportedly improves on conventional immunoturbidimetric detection by more than three orders of magnitude in a compact optical format, illustrating that non-electrochemical transduction can also be miniaturized to approach or exceed the sensitivity of the very clinical-laboratory method that POC devices seek to replace [17]. Across these platforms, the recurring engineering strategy is the same: use capillary-driven or pump-driven microfluidic architectures to handle nanoliter-to-microliter blood volumes and automate plasma separation, then couple the processed sample to a transduction layer—electrochemical, plasmonic, or colorimetric—engineered for the sub-milligram-per-liter sensitivity clinically required for hs-CRP interpretation [11]. A practical consequence of embedding plasma separation on-chip, as in the sedimentation-and-filtration approach of Lai and colleagues, is that these devices can in principle accept a finger-prick or small venous draw of whole blood directly, avoiding the centrifugation step that otherwise ties conventional immunoturbidimetric testing to a staffed clinical laboratory [12]. The multiplexed wave-shaped chip further illustrates that once plasma separation and microfluidic transport are solved, extending a single-analyte CRP chip to a small inflammatory biomarker panel is primarily a matter of adding parallel detection zones rather than redesigning the underlying fluidics [13].

Table 1: Representative published microfluidic and point-of-care CRP platforms by detection principle, sample type, and reported assay time.

Platform / Reference	Detection principle	Sample matrix	Reported assay time
Lai et al. 2022 [12]	On-chip plasma extraction + electrochemical hs-CRP	Whole blood	~40 min
Yin et al. 2022 [13]	Wave-shaped multiplex microfluidic chip	Whole blood / serum	~22 min
Chen et al. 2024 [14]	Microfluidic sandwich-ELISA colorimetric	Urine	~50 min
Dong et al. 2017 [21]	Paper-based colorimetric + smartphone	Whole blood	~15 min
Boonkaew et al. 2024 [15]	NFC smartphone electrochemical microfluidic	Serum/plasma	Not fully specified

Figure 1: Illustrative order-of-magnitude limits of detection reported for CRP point-of-care transduction modalities relative to clinical immunoturbidimetric assays. Values are representative typical ranges drawn from the reviewed literature, not measurements from a single study, and are plotted on a logarithmic scale.



Paper-Based and Optical Point-of-Care CRP Assays

Paper-based microfluidics, pioneered as a low-cost diagnostic substrate for resource-limited settings, has been a particularly active platform for CRP POC testing [18,19,20]. Dong and colleagues built a smartphone-integrated, paper-based microfluidic "CRP-Chip" that produced results within 15 minutes for an estimated material cost of under 50 US cents, with concordance against standard laboratory methods, directly

demonstrating the low-cost promise of the paper microfluidics paradigm for chronic-disease and infection screening [21]. Building on colorimetric paper devices, Ning and colleagues applied a machine-learning image-analysis pipeline—using a You-Only-Look-Once (YOLO) object-detection model to localize the reaction zone followed by a residual-network classifier—to a paper-based microfluidic CRP assay, achieving 96% accuracy for CRP-based risk stratification and showing how computer vision can compensate for the semi-quantitative nature of colorimetric strip readouts [22].

Table 2: Detection-modality comparison for CRP point-of-care biosensing reviewed in this article.

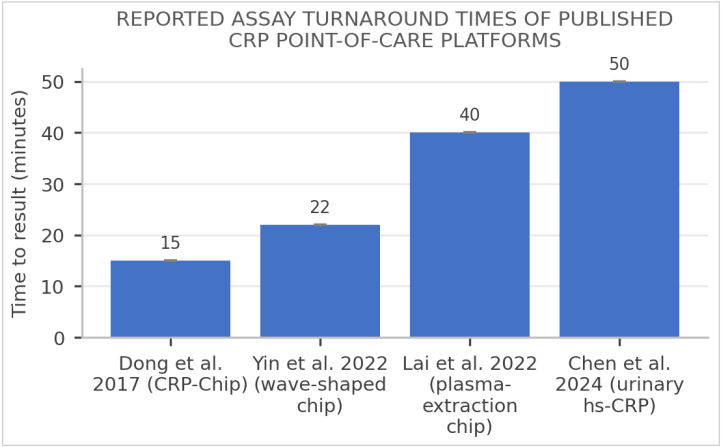
Modality	Representative platforms	Key advantage	Key limitation
Electrochemical microfluidic	[12,16,15]	High sensitivity, on-chip plasma separation	Electrode fabrication and reagent stability
Optical (SPR / plasmonic)	[23,24,17]	Label-free, very high sensitivity achievable	Bulkier optics, higher instrument cost
Paper-based colorimetric	[21,22]	Very low cost, disposable, smartphone-readable	Lower analytical sensitivity, semi-quantitative
Smartphone diffusometric / fluorescence	[25]	No dedicated benchtop instrument required	Requires fluorescent labeling reagents

Optical label-free transduction has been explored extensively as an alternative to colorimetric or electrochemical readout. Wang and colleagues developed a disposable fiber-optic surface plasmon resonance (SPR) biosensor for CRP using polydopamine-mediated antibody immobilization, reporting a strong linear response across a clinically relevant concentration range while retaining the low-cross-contamination advantage of single-use fiber probes [23]. A broader review by Seok and Ju surveyed plasmonic optical biosensors for CRP, contrasting propagating surface-plasmon-resonance platforms on planar metal films with localized surface-plasmon-resonance platforms on metal nanostructures, and concluded that conventional SPR sensors generally achieved lower limits of detection than nanostructure-based localized SPR sensors, while the latter offered simpler, more portable optical configurations [24]. Smartphone-based diffusometric immunoassays represent a further miniaturization of optical detection: Chuang and colleagues coupled a smartphone-mounted fluorescence attachment to antibody-functionalized fluorescent nanobeads, inferring CRP concentration from antigen-induced changes in nanobead diffusivity measured via fluorescence correlation spectroscopy, achieving a linear sensing range spanning several micrograms per milliliter without any dedicated benchtop instrumentation [25]. Collectively, these paper-based and optical strategies emphasize accessibility and instrument-free or smartphone-only operation, generally trading some analytical sensitivity for dramatically lower cost and hardware complexity relative to electrochemical microfluidic platforms.

Clinical Validation and Implementation Considerations

Ultimately, the value of any microfluidic CRP platform is judged against the immunoturbidimetric and immunonephelometric assays that remain the clinical laboratory reference standard, and against the clinical outcomes such testing is meant to influence. A comprehensive recent review of CRP testing methods surveyed the trajectory from these established clinical-chemistry techniques through emerging point-of-care biosensor formats, underscoring that analytical agreement with laboratory-grade immunoturbidimetry, not just raw sensitivity, is the benchmark that determines clinical adoption [26]. On the outcomes side, a randomized controlled trial by Cals and colleagues found that point-of-care CRP testing in primary care reduced antibiotic prescribing for respiratory tract infections [5], a finding reinforced by a systematic review and meta-analysis of randomized controlled trials showing consistent reductions in antibiotic use associated with CRP POC testing across primary-care settings [6], and by a cluster-randomized trial demonstrating a similar benefit specifically among nursing home residents with lower respiratory tract infections [7]. Together, these trials provide the clinical justification for continued microfluidic device development: a technology that can deliver laboratory-concordant CRP results within minutes at the bedside has a demonstrated pathway to altering prescribing behavior and, by extension, antimicrobial stewardship.

Figure 2: Reported assay turnaround times for four published microfluidic/paper-based point-of-care CRP platforms, from sample application to result [21,13,12,14].



Realizing that potential at scale, however, has historically been constrained less by biosensor chemistry than by manufacturing, regulatory, and usability barriers. Chin, Linder, and Sia's analysis of the commercialization of microfluidic point-of-care diagnostics highlighted that few academically demonstrated microfluidic assays progress to regulated, manufactured products, citing challenges in reagent stability, low-cost mass fabrication, and integration with a robust reader ecosystem [9]. Vashist and colleagues likewise emphasized that next-generation point-of-care testing depends as much on connectivity, data management, and manufacturability as on sensor sensitivity [10], while earlier foundational work by Yager and colleagues framed point-of-care diagnostics for global health around the need for assays that are simultaneously sensitive, low-cost, and operable without trained personnel or laboratory infrastructure [8]. The CRP literature reviewed here illustrates that microfluidic devices have made substantial progress on analytical performance and assay time; translating that progress into widely deployed clinical tools will depend on continued attention to these non-biosensing engineering and health-systems constraints.

Conclusion

Published literature on microfluidic and related point-of-care CRP platforms demonstrates convergent progress toward the goal of laboratory-concordant, whole-blood CRP quantification within

minutes rather than hours. Electrochemical microfluidic chips, paper-based colorimetric and machine-learning-assisted strips, and optical platforms spanning fiber-optic SPR, nanoplasmonic immunoturbidimetry, and smartphone diffusometry each offer a distinct balance of sensitivity, cost, and hardware complexity, but all report assay times on the order of 15 to 50 minutes—markedly faster than conventional laboratory turnaround inclusive of sample transport. The strongest evidence for clinical impact comes not from any single biosensor but from randomized trials and meta-analyses showing that point-of-care CRP testing changes antibiotic-prescribing behavior in primary care and nursing home settings. Future work integrating the analytical gains reviewed here with manufacturable, connected device platforms will be necessary to move microfluidic CRP testing from demonstrated laboratory prototypes into routine point-of-care practice.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Zielinski P conceived the review, conducted the literature search, and drafted the manuscript. Dahl I contributed to the literature screening and technical framing and critically revised the manuscript for important intellectual content. Russo R contributed additional context and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

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