Comparison of point-of-care HbA1c devices with laboratory HPLC methods: A systematic review and meta-analysis

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Received July 7, 2025; Accepted Feruary 4, 2026

DOI: 10.3892/br.2026.2120

Abstract. Hemoglobin A1c (HbA1c), also known as glycated hemoglobin, is a cornerstone biomarker for diagnosing and monitoring diabetes. While high-performance liquid chromatography (HPLC) is the reference standard, point-of-care (POC) devices are increasingly used due to convenience and rapid results. However, concerns remain about their analytical accuracy. This systematic review and meta-analysis evaluated the agreement between POC HbA1c devices and laboratory HPLC-based methods. A total of 11 studies involving 1,593 participants and 3,285 paired measurements were included. The pooled mean difference between POC and HPLC was 0.01% [95% confidence interval (CI), -0.08 to 0.11%; 95% prediction interval (PI), -0.443 to 0.471%; P=0.779], well within the clinically acceptable margin of ±0.5%. However, substantial heterogeneity was observed and extensive subgroup analyses across device model, analytical principle, and study characteristics did not fully explain this variability. Notably, some platforms, such as lateral flow immunoassays, exhibited larger biases approaching thresholds relevant to clinical decision-making. Although most POC devices demonstrated acceptable agreement, results highlight the importance of careful validation and interpretation. Future research should prioritize standardized protocols, comparative studies across platforms, and assessment in real-world decentralized settings to enhance confidence in POC HbA1c measurement.

Introduction

Diabetes mellitus represents one of the most pressing global health challenges of the 21st century. According to the International Diabetes Federation, the number of individuals living with diabetes is projected to reach 783 million by 2045 (1). This rising prevalence highlights the substantial public health impact of diabetes, which leads to serious complications such as cardiovascular disease, nephropathy, and retinopathy, and in turn contributes to reduced quality of life and increased morbidity. These complications place a significant burden on healthcare systems and economies worldwide (2). Early diagnosis and regular monitoring are therefore essential to prevent long term complications, optimize glycemic control, and improve clinical outcomes (3).

Hemoglobin A1c (HbA1c), commonly referred to as glycated hemoglobin is widely recognized as a critical biomarker for both the diagnosis and long-term monitoring of diabetes. A threshold of 6.5% is recommended by international guidelines for diagnostic purposes (4). HbA1c remains the gold standard for assessing glycemic control, as it reflects average plasma glucose over the preceding 2 to 3 months (5).

High-performance liquid chromatography (HPLC)-based devices are regarded as the reference method for HbA1c measurement, owing to their high precision, reproducibility, and compatibility with long-term standardization programs (6). Although HPLC-based devices offer rapid and precise measurements, the requirement for costly instrumentation, technical expertise, and centralized laboratory infrastructure often renders them impractical in primary care environments or underserved regions with limited resources and low testing volumes.

To overcome these limitations, point-of-care (POC) HbA1c devices have been increasingly adopted. These devices enable rapid, on-site testing using small blood samples obtained via finger prick or venous sampling, and can be operated by non-laboratory personnel (7). A variety of POC HbA1c devices have been developed, employing distinct analytical principles. Commonly used systems include the DCA Vantage (latex-enhanced immunoassay), Afinion AS100 (boronate affinity chromatography), and Quo-Test (boronate affinity fluorometry) (8). Despite their convenience and increasing use in outpatient and community settings, these platforms differ substantially in detection chemistry, susceptibility to analytical interference (such as hemoglobin variants), and calibration stability. These factors may contribute to inconsistencies in measurement accuracy. Notably, deviations near key clinical thresholds, such as 6.5% for diagnosis or 7.0-8.0%

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Key words: diabetes, hemoglobin A1c, high-performance liquid chromatography, instrument performance, point-of-care

for treatment decisions, may result in misclassification and inappropriate therapeutic interventions (9,10).

Given the increasing clinical reliance on POC testing, a comprehensive evaluation of their agreement with reference HPLC-based methods is essential. While several studies have assessed individual device performance, results remain inconsistent (11,12). For example, a prior meta-analysis reported substantial variability in bias across different POC platforms, with some devices showing deviations beyond clinically acceptable limits (10). Although international standardization efforts, led by the National Glycohemoglobin Standardization Program (NGSP) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), have significantly improved the comparability of HbA1c results, the diversity of analytical principles employed by POC devices continues to pose challenges for ensuring consistent accuracy across platforms (13-15).

The aim of this systematic review and meta-analysis was to systematically assess the agreement between POC and HPLC-based laboratory methods for HbA1c measurement. Data on mean differences were pooled, subgroup analyses were conducted to explore heterogeneity, and device-specific factors that may affect measurement reliability were investigated. The findings are intended to inform clinicians, policymakers, and healthcare providers about the practical utility of POC HbA1c testing in routine diabetes care.

Materials and methods

Study design and registration. This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (16). The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration no. CRD420251063197).

Search strategy and study selection. A comprehensive literature search was conducted in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com), Web of Science (https://clarivate.com/), and Cochrane Library (https://www.cochranelibrary.com) to identify relevant studies published between January 2015 and April 2025. Search terms included combinations of 'HbA1c', 'glycated hemoglobin', 'point-of-care', 'POC', 'HPLC', and 'high performance liquid chromatography'. The detailed search strategies for each database are provided in the Table SI.

Studies were eligible for inclusion if they i) were original research articles directly comparing HbA1c measurements obtained from POC devices and HPLC-based laboratory methods in the same patient population, and ii) reported at least one agreement metric, such as the mean difference between methods, 95% limits of agreement (LoA), or a Bland-Altman analysis. Among these studies, only those with sufficient numerical data available to extract or derive quantitative agreement measures were included in the quantitative synthesis. Exclusion criteria included reviews, case reports, conference abstracts without extractable data, animal studies, and studies using non-HPLC methods as the reference.

Two reviewers (YW and MG) independently screened titles, abstracts, and full texts. Disagreements were resolved by discussion or, when necessary, by consultation with a third reviewer (ZH).

Quality assessment. The methodological quality of the included studies was assessed using the QUADAS-2 tool (Table SII), which evaluates four domains: Patient selection, index test, reference standard, and flow and timing (17).

Data extraction. For each included study, the following information was extracted: Author, publication year, country, sample size, specimen type (capillary or venous), POC device, POC assay principle, reference HPLC-based device and HPLC assay principle. Outcomes of interest included the mean difference (bias) between POC and HPLC as the primary outcome, as well as standard deviation (SD) of the bias, and 95% LoA, which were used to characterize measurement variability and to derive confidence and prediction intervals (18,19). For quantitative synthesis, all method comparison metrics were harmonized to a common effect size defined as the mean difference (POC-HPLC) in % HbA1c. If not directly reported, LoA were calculated as the mean difference ±1.96 x SD. When only the 95% confidence interval (CI) for the mean difference was available, the SD was back-calculated using the CI formula, assuming normal distribution and known sample size. Studies reporting only graphical Bland-Altman plots without extractable numerical data were excluded from quantitative synthesis.

Data extraction was independently performed by two reviewers (YW and MG) using a standardized template. Any discrepancies were resolved through discussion.

Statistical analysis. All statistical analyses were performed using Stata version 18.0 (StataCorp LP). A random-effects model [restricted maximum likelihood (REML)] was used to pool mean differences between POC and HPLC measurements. The null hypothesis tested was that the pooled mean difference equals zero. All statistical tests were two-sided, with a significance level of 0.05. To obtain robust inference under substantial heterogeneity, Hartung-Knapp adjustments were applied to all pooled confidence intervals. In addition to the pooled 95% CI, a 95% prediction interval (PI) was calculated to reflect the expected dispersion of true effects in future clinical settings (20,21).

Between-study heterogeneity was assessed using Cochran's Q test, the I^2 statistic, and τ^2. Potential sources of heterogeneity were explored by subgroup analyses and univariable random-effects meta-regression with REML estimation and Hartung-Knapp adjustment. Meta-regression analyses were conducted for several moderators, including device analytical principle, specimen type (capillary, venous), study setting, study-level risk of bias, variant exclusion, funding source, POC model, and HPLC analytical principle. Furthermore, for studies which contributed more than one comparison, within study correlation was addressed using robust variance estimation (RVE) as a sensitivity analysis (22). A leave-one-out influence analysis was performed to evaluate the impact of individual studies on the pooled estimate (23). Small study effects were assessed using Egger's test, complemented by visual inspection of funnel plots and, where applicable,

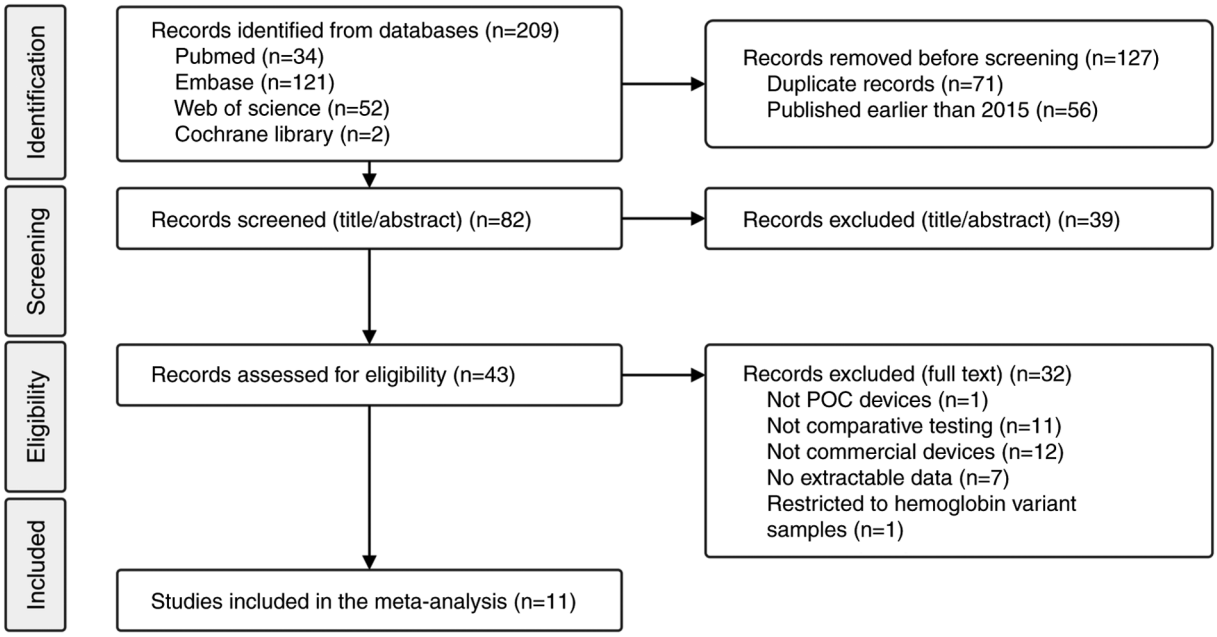

Figure 1. PRISMA flow diagram. PRISMA flow diagram summarizing the identification, screening, eligibility assessment, de-duplication, and final inclusion of studies comparing POC HbA1c devices with laboratory-based HPLC. The search covered four databases (PubMed, Embase, Web of Science, and Cochrane Library) from January 2015 to April 2025, with English-language restrictions. Reasons for exclusion at the full-text stage are reported in the diagram. POC, point-of-care; HbA1c, hemoglobin A1c.

trim-and-fill procedures, with results interpreted cautiously in the context of substantial heterogeneity (24).

The pooled results are also presented in mmol/mol according to IFCC reporting standards. Specifically, to convert the pooled mean difference from percentage units to mmol/mol, the following formula was applied: HbA1c (mmol/mol)=(HbA1c (%) -2.15) x10.93.

Protocol deviations. The final analysis included several methodological refinements that were not fully prespecified in the registered PROSPERO protocol. Although the protocol initially planned to assess certainty of evidence using the GRADE framework, a formal GRADE evaluation was not performed in the final manuscript (25). Instead, methodological quality of individual studies was assessed using the QUADAS-2 tool, which is more appropriate for method-comparison studies focusing on analytical agreement. In addition, the statistical analysis plan was refined to incorporate more robust, model-based approaches and sensitivity analyses to address substantial heterogeneity and non-independence, including REML-based random-effects modeling with Hartung-Knapp-adjusted inference, PI, leave-one-out influence analysis, and RVE for within-study clustering.

Results

Characteristics of included studies. A PRISMA flow diagram was used to document the screening process and reasons for exclusion (Fig. 1). A total of 209 records were retrieved from the initial database search. After removing duplicates, excluding articles published before 2015, and screening titles, abstracts, and full texts, a total of 11 studies met the inclusion criteria and were included in the final meta-analysis (11,12,26-34). These studies encompassed 1,593 participants and provided 3,285 paired HbA1c measurements comparing POC devices with reference HPLC-based laboratory methods.

As summarized in Table I, with additional details provided in Table SIII, the included studies were published between 2015 and 2024, with sample sizes ranging from 40 to 514 participants. A wide range of POC devices were evaluated, including B-Analyst (The Menarini Group), DCA Vantage (Siemens Healthineers AG), Afinion AS100 (Abbott), Quo-Test (EKF Diagnostics Holdings plc), Cobas b101 (Roche Diagnostics), A1C EZ 2.0 (Wuxi Biohermes Bio & Medical Technology Co., Ltd.), HemoCue HbA1c 501 (HemoCue AB), Tri-stat POC (Trinity Biotech Plc), and i-Chroma (Boditech Med Inc.), representing various analytical principles such as immunoassay and boronate affinity chromatography. Based on analytical principles, four devices employed immunoassay-based methods, including B-Analyst, Cobas b101, and DCA Vantage, which utilize latex agglutination immunoassays, as well as i-Chroma, which uses a fluorescence-based lateral flow immunoassay. The remaining five devices were based on boronate affinity chromatography. Regarding the reference methods, six of the HPLC-based devices used in the included studies employed ion-exchange chromatography, while one device used boronate affinity chromatography combined with HPLC (Table I).

Meta-analysis of mean bias. The pooled mean difference (bias) between POC and HPLC methods across all included studies was 0.01% (95% CI: -0.08% to 0.11%; P=0.779) (Fig. 2), corresponding to 0.1 mmol/mol on the IFCC scale. Although the pooled bias was clinically negligible, between-study heterogeneity was substantial (τ^2=0.04; I^2=98.96%). The 95% PI ranged from -0.44% to 0.47% (Fig. 2), spanning the clinically acceptable margin of ±0.5% (35).

Table I. Characteristics of included studies.

First author/s, year	Country	No. of patients	Variant	POC device	POC principle	Comparator device	(Refs.)
Menéndez-Valladares *et al*, 2015	Spain	114	Excluded	B-Analyst	Immuno-assay	Arkray HA-8180	(26)
Criel *et al*, 2016	Belgium	40	Not clear	Cobas b101 Afinion B-Analyst	Immuno-assay Boronate affinity Immuno-assay	Arkray HA-8160	(11)
Grant *et al*, 2017	UK	100	Not clear	Quo-Test	Boronate affinity	BioRad D10	(12)
Wang *et al*, 2018	China	514	Excluded	A1C EZ 2.0	Boronate affinity	BioRad Variant II Tosoh G8 Trinity Premier Hb9210	(27)
Dupuy *et al*, 2019	France	110	Not clear	Cobas b101	Immuno-assay	Tosoh G8	(28)
Dubach *et al*, 2019	Switzer-land	100	Not clear	Afinion DCA	Boronate affinity Immuno-assay	Tosoh G8	(29)
Guadalupe Vargas *et al*, 2020	Ecuador	114	Excluded	DCA i-Chroma	Immuno-assay Immuno-assay	BioRad Variant II	(30)
Şahingöz Erdal *et al*, 2019	Turkey	77	Excluded	Tri-stat POCT	Boronate affinity	Trinity Premier Hb9210	(31)
Toro-Crespo *et al*, 2017	Spain	100	Not clear	Afinion B-Analyst	Boronate affinity Immuno-assay	Tosoh G8	(32)
Rathod *et al*, 2024	India	121	Not clear	HemoCue	Boronate affinity	Tosoh GX	(33)
Saxton *et al*, 2018	USA	203	Not clear	Afinion DCA	Boronate affinity Immuno-assay	Trinity Premier Hb9210	(34)

Characteristics of included studies comparing POC HbA1c devices with laboratory HPLC-based reference methods. B-Analyst (The Menarini Group); Cobas b101 (Roche Diagnostics); Afinion (Abbott); Quo-Test (EKF Diagnostics Holdings plc); A1C EZ 2.0 (Wuxi Biohermes Bio & Medical Technology Co., Ltd.); DCA (Siemens Healthineers AG); i-Chroma (Boditech Med Inc.); Tri-stat POCT and Trinity Premier Hb9210 (Trinity Biotech Plc); HemoCue (HemoCue AB); Arkray HA-8160 and HA-8180 (Arkray, Inc.); Bio-Rad D-10 and Variant II (Bio-Rad Laboratories, Inc.); Tosoh G8 and GX (Tosoh Bioscience). Ion exchange, ion-exchange chromatography; immunoassay, antibody- or antigen-based assay methods; boronate affinity, assays based on boronate affinity chromatography; boronate affinity (HPLC), boronate affinity chromatography combined with HPLC. POC, point-of-care; HbA1c, hemoglobin A1c; HPLC, high-performance liquid chromatography.

Notably, most POC devices demonstrated minimal systematic bias; however, device-specific variability was observed. Notably, the i-Chroma system exhibited the largest individual deviation, with a mean difference of -0.50% (95% CI, -0.80 to -0.20%), approaching or exceeding thresholds relevant to clinical decision-making.

Exploring heterogeneity. To investigate potential sources of heterogeneity, subgroup analyses by POC device model and analytical principle were performed (Figs. 3 and 4). Most device-specific subgroups demonstrated pooled biases within the clinically acceptable range of ±0.5%; however, substantial heterogeneity persisted. When stratified by analytical principle, non-chromatographic immunoassay platforms demonstrated a pooled bias of -0.02% (95% CI, -0.11 to 0.15%; τ^2=0.03; I^2=98.73%). Because i-Chroma employs an immunochromatographic (lateral-flow) format with distinct analytical characteristics, it was evaluated separately rather than being combined with other immunoassay-based platforms. Boronate affinity-based devices showed a pooled bias of 0.04% (95% CI, -0.09 to 0.17%; τ^2=0.05; I^2=98.99%).

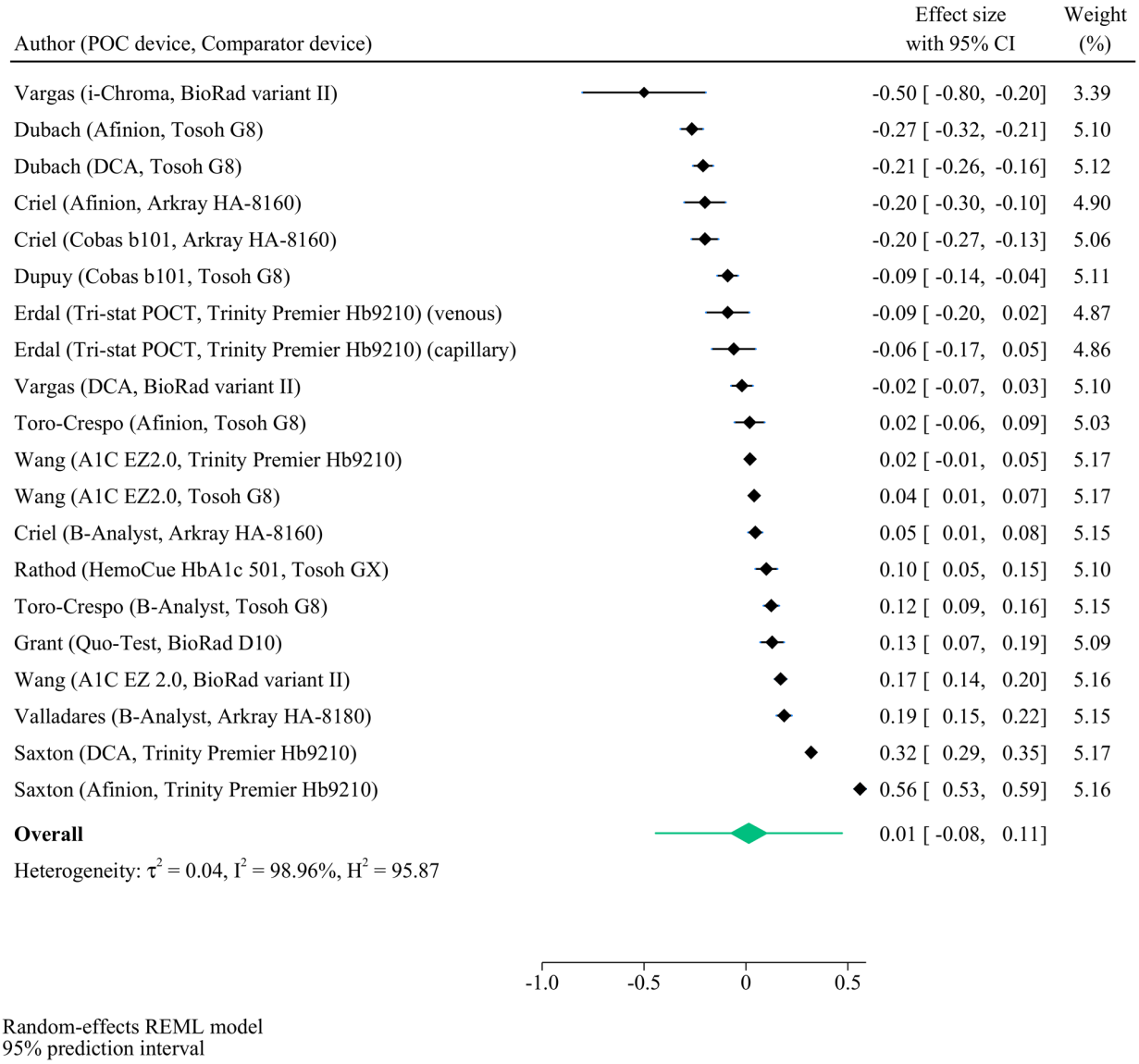

Figure 2. Forest plot overall. Forest plot displaying the mean difference in % HbA1c (POC-HPLC) with corresponding 95% CI for each device comparison. Estimates were synthesized using a random-effects model fitted with REML and Hartung-Knapp adjustment. Study weights are shown, and individual comparisons are ordered by mean bias. The pooled effect is presented with its 95% CI and 95% PI. Heterogeneity statistics, including I^2 and τ^2, are reported within the figure [Q (df=19)=1,810.74]. HbA1c, hemoglobin A1c; POC, point-of-care; HPLC, high-performance liquid chromatography; REML, restricted maximum likelihood; CI, confidence interval; PI, prediction interval.

Additional subgroup analyses stratified by specimen type, reference-method analytical principle, exclusion of hemoglobin variants, study setting, study-level risk of bias, and funding source are presented in Figs. S1-6. The statistical data for these analyses, including results in both % HbA1c and mmol/mol units, are summarized in Table SIV. Across all subgroup analyses, heterogeneity remained consistently high, indicating that stratification by a single study-level characteristic did not materially reduce between-study variability.

To further explore determinants of heterogeneity, univariable random-effects meta-regression models with Hartung-Knapp adjustment were fitted for study- and device-level moderators (Table SV). As a result, study setting explained the largest share of between-study variance (R^2=20.6%), with decentralized testing associated with higher positive bias (borderline, P=0.067). POC analytical principle accounted for a modest share of variance (R^2=6.4%; P=0.15), while HPLC analytical principle explained R^2=11.2% (P=0.10).

Other moderators, including specimen type, funding source, reporting of hemoglobin variants, study-level risk of bias, and individual POC brands or models, explained virtually none of the between-study variability (all R^2≤5%; P>0.10; Table SV). Furthermore, across all models, substantial residual heterogeneity remained (residual heterogeneity, P<0.001), indicating that no single examined moderator sufficiently accounted for the extreme dispersion of effects.

Sensitivity analysis and robustness. To address potential non-independence among multiple effect sizes derived from the same primary studies, RVE was applied as a sensitivity analysis. The RVE-adjusted pooled mean difference was 0.03% HbA1c (95% CI, -0.11 to 0.16%; P=0.683; data not shown), which was directionally and quantitatively consistent

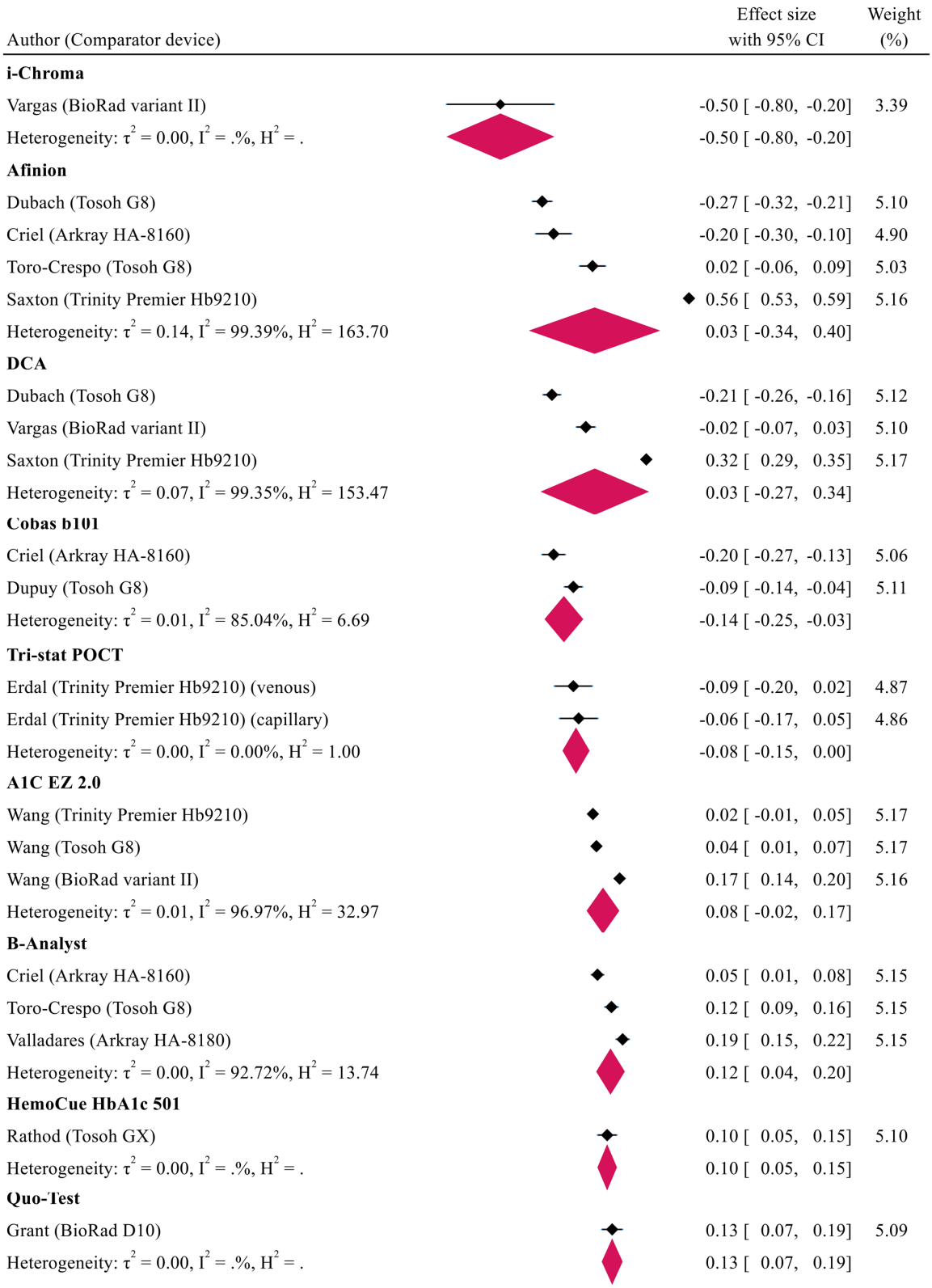

Figure 3. Subgroup by POC device model. Forest plot of mean difference in % HbA1c (POC-HPLC) with 95% CI, pooled within each POC device model and ordered by subgroup mean bias. Subgroup estimates were generated using a random-effects model fitted with REML and Hartung-Knapp adjustment. Corresponding heterogeneity statistics for each subgroup are reported in Table SIV. POC, point-of-care; HbA1c, hemoglobin A1c; HPLC, high-performance liquid chromatography; CI, confidence interval; REML, restricted maximum likelihood.

with the primary random-effects model. This indicates that within-study clustering did not materially influence the pooled inference. Leave-one-out influence analyses showed that removal of any single comparison did not materially change the pooled mean difference (range of re-estimated MDs: -0.01% to 0.03%) (Table SVI). The 95% CIs consistently crossed zero, and τ^2 and I^2 remained high across iterations, indicating that no individual study drove the observed heterogeneity.

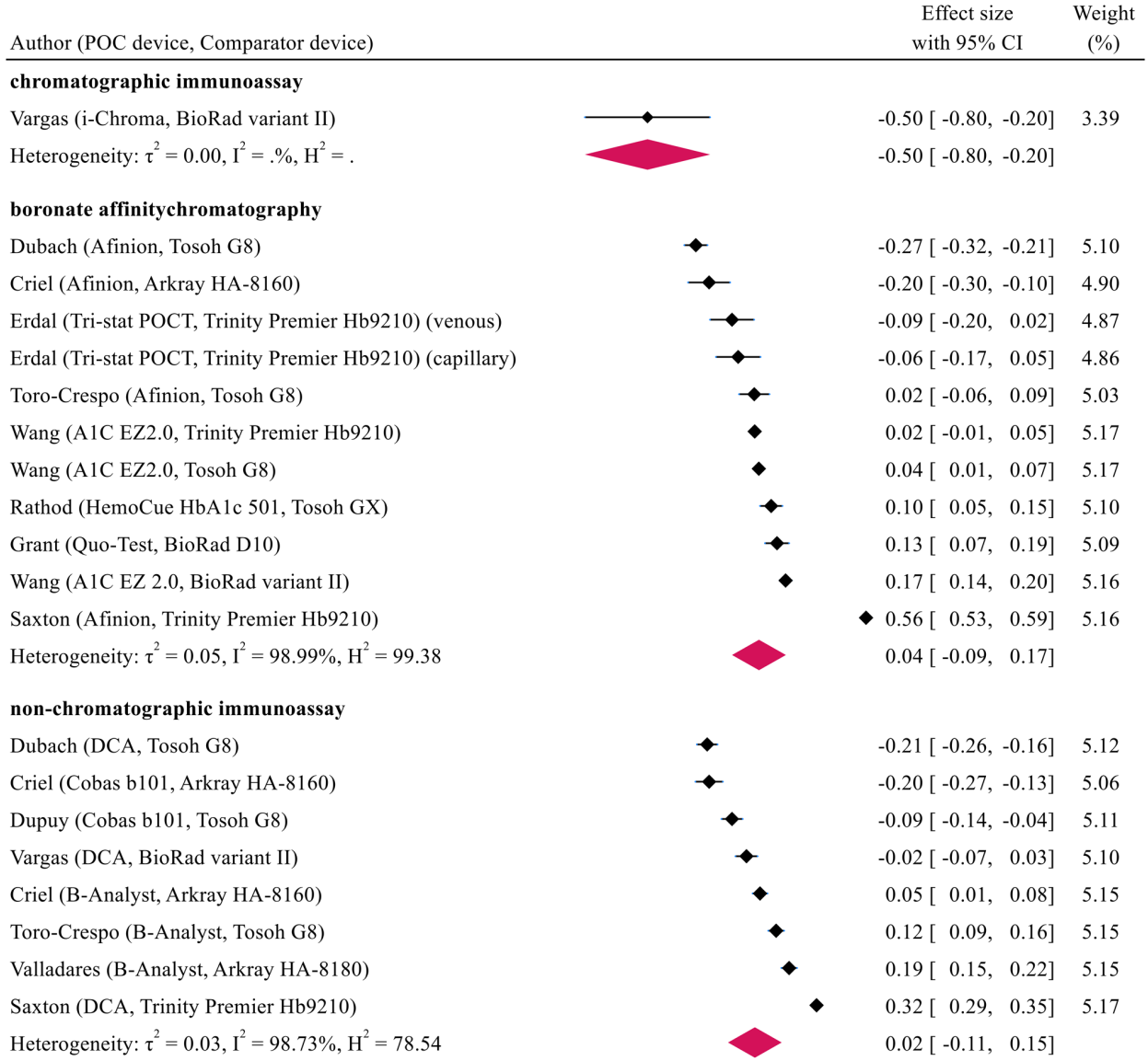

Figure 4. Subgroup by POC analytical principle. Forest plot of mean difference in % HbA1c (POC-HPLC) with 95% CI, pooled within each analytical principle of POC devices and ordered by subgroup mean bias. Subgroup estimates were generated using a random-effects model fitted with REML and Hartung-Knapp adjustment. Corresponding heterogeneity statistics for each subgroup are reported in Table SIV. POC, point-of-care; HbA1c, hemoglobin A1c; HPLC, high-performance liquid chromatography; CI, confidence interval; REML, restricted maximum likelihood.

Publication bias assessment. Publication bias was evaluated using Egger's regression test and visualized using a funnel plot of 20 device-level comparisons. Egger's regression test indicated possible small-study effects (P<0.001). However, given the extreme between-study heterogeneity, this finding was interpreted cautiously because Egger's test may yield spurious significance under such conditions. Visual inspection of the funnel plot did not reveal a clear pattern of asymmetry (Fig. S7). In trim-and-fill sensitivity analyses, no studies were imputed (imputed=0), and the pooled estimate remained unchanged (observed MD=0.01% vs. adjusted MD=0.01%; data not shown), supporting the robustness of the primary findings.

Although Egger's test indicated small-study asymmetry, this likely reflects between-study dispersion rather than selective publication, as trim-and-fill did not impute missing studies and the pooled estimate was unchanged.

Discussion

The present systematic review and meta-analysis evaluated the agreement between POC HbA1c devices and laboratory HPLC-based methods, which are widely regarded as the reference standard for glycated hemoglobin measurement (6). Across 11 eligible studies comprising 3,285 paired measurements, it was found that most POC devices demonstrated acceptable agreement with HPLC, yielding a pooled mean difference of 0.01% (95% CI, -0.08 to 0.11%; P=0.779). This level of bias falls well within the clinically accepted margin of ±0.5%, suggesting that contemporary POC devices can provide clinically usable HbA1c measurements under appropriate conditions.

Notably, the 95% PI around the pooled estimate spanned nearly the full ±0.5% clinically acceptable margin and extended across the 6.5% diagnostic cut-off. This indicates

that, although average agreement is favorable, individual devices or settings may yield values on opposite sides of the diagnostic threshold, particularly for patients near 6.5%. Therefore, even small systematic differences warrant careful interpretation at the individual-patient level.

However, the substantial heterogeneity across studies (I^2 ~99.0%; Table SIV) indicates that the pooled estimate represents an average effect across diverse devices and settings rather than evidence of analytical interchangeability. Device-specific factors, testing environments, and patient characteristics therefore require careful consideration when interpreting individual results.

While some earlier studies documented devices with clinically unacceptable bias, our findings, excluding the i-Chroma, indicate that the majority of POC platforms meet the ±0.5% criterion for clinical agreement (10). This observation aligns with a previous meta-analysis which noted a non-significant trend toward less negative bias over time for the DCA device (coefficient 0.01% HbA1c per year; P=0.081), suggesting possible calibration improvements, although no significant temporal effect was observed for other devices (10,36,37). The findings of the present study reinforce this improvement and underscore the importance of device-specific evaluation, particularly for platforms such as lateral-flow chromatographic assay.

In addition, while a ±0.5% difference may be acceptable for population-level agreement, such variation could accumulate over time and influence longitudinal monitoring, particularly when clinical management relies on small changes in HbA1c.

Subgroup analyses provided additional insight but did not fully account for the substantial heterogeneity observed across studies. Stratification by device type, analytical principle, reference HPLC method, funding, exclusion of hemoglobin variants, specimen type, study setting, and other factors did not substantially reduce variability (Figs. 3, 4, and S1-6). This likely reflects the complex interplay of multiple factors inherent to *in vitro* diagnostic testing, including differences in reagent lots, calibration protocols, operator training, and environmental conditions. Previous reviews have emphasized that such variability remains a persistent challenge in standardizing HbA1c measurement across platforms and settings (10,35). Therefore, subgroup findings should be interpreted cautiously, and further large-scale standardized evaluations are needed to clarify sources of inconsistency.

Although the observed performance differences were not statistically attributable to analytical method, the underlying detection principles offer a useful framework for interpreting variability across devices. Boronate affinity chromatography, employed by devices such as Afinion and A1C EZ 2.0, targets cis-diol structures of glycated residues, regardless of glycation site (38). Although this method is generally robust and less affected by hemoglobin variants, its broader detection scope theoretically includes multiple glycated species beyond the IFCC-defined β-N-terminal glycation (38,39).

Notably, although manufacturer-level calibration can align these signals to the IFCC scale, the inherent detection characteristics of the method may introduce upward bias if non-target glycation is not sufficiently constrained. Therefore, potential method-based discrepancies in accuracy relate less to whether calibration occurs, and more to how tightly the underlying chemistry supports IFCC-conformant measurement.

By contrast, immunoassay-based methods depend on antibody specificity for HbA1c, making them more vulnerable to epitope changes, masking, or variant interference (40). Particularly, devices using lateral-flow formats add complexity due to open-system operation and manual handling, which may further compromise quantitative precision. While lateral-flow formats offer advantages in portability and ease of use, they are generally less precise due to their susceptibility to flow dynamics, operator variability, and lower analytical sensitivity (41). In addition, although enzymatic methods are widely used in centralized laboratories and rely on endoglycosidase digestion followed by quantification of released glycated amino acids, no studies of enzymatic POC platforms met our inclusion criteria (42-44). Consequently, the findings of the present study may not be generalizable to enzymatic systems, underscoring an important gap in the current evidence base.

From a practical standpoint, some studies evaluated POC devices using venous blood instead of capillary fingerstick samples, despite the devices being designed for the latter (30,33). While venous sampling improves methodological consistency and reduces pre-analytical variation, it may underestimate real-world variability. In decentralized settings, several additional factors may contribute to reduced accuracy, including operator training, sample collection technique, time from sampling to analysis, ambient environmental conditions (including temperature and humidity), and adherence to device-specific quality control protocols (13). Variability may also be amplified when testing is performed by non-laboratory personnel in community clinics, pharmacies, or home settings. Thus, analytical performance demonstrated under controlled conditions may not fully reflect achievable accuracy in routine practice.

An additional concern is analytical interference from hemoglobin variants or elevated fetal hemoglobin. Hemoglobin variants are genetically inherited structural alterations in the globin chains, commonly resulting from point mutations, deletions, or amino-acid substitutions. These variants include clinically prevalent types such as HbS (sickle cell), HbC, HbE, and HbD, which occur at relatively high frequencies in individuals of African, Mediterranean, and Southeast Asian descent (45). Depending on the nature and location of the mutation, these variants may interfere with HbA1c measurement through multiple mechanisms: Altering the glycation site, affecting the charge or conformation of the protein, or modifying red blood cell lifespan (46). Beyond structural variants, conditions associated with altered erythrocyte turnover, such as anemia or chronic kidney disease, may also bias HbA1c values independent of analytical method.

Therefore, in individuals with suspected or known hemoglobinopathies, HbA1c should be interpreted with caution, and alternative markers such as glycated albumin or fructosamine may be more appropriate. Clinically, the presence of hemoglobin variants significantly limits the reliability of HbA1c measurements. As a result, the standard diagnostic cutoff of 6.5% may not be valid in these populations. Guidelines from the ADA and WHO recommend alternative diagnostic approaches, such as fasting glucose, OGTT, or short-term glycation markers (such as fructosamine and glycated albumin), when hemoglobinopathies are suspected or confirmed (47,48). Notably, ion-exchange method and capillary electrophoresis

can provide variant information on the result graph, which provides an essential clinical application (49).

The present study has several strengths, including a comprehensive search strategy, strict inclusion criteria requiring HPLC as the reference standard, and the use of standardized agreement metrics. Subgroup analyses were conducted, and pooled estimates remained consistent across analytic approaches, supporting the robustness of our findings. However, certain limitations should be noted. The number of included studies was relatively small, and several devices were represented by only one or two datasets, limiting statistical power and generalizability. Numerous studies lacked detailed reporting on calibration protocols, quality control measures, and management of analytical interference. Additionally, our analysis focused primarily on analytical agreement rather than diagnostic accuracy, clinical outcomes, or cost-effectiveness, which are critical for real-world adoption.

Future research should prioritize large-scale implementation studies that assess device performance in decentralized settings, account for operator variability, and evaluate resilience under environmental stressors such as temperature and humidity. Head-to-head comparative studies across multiple platforms and integration of advanced calibration technologies, including AI-assisted algorithms and real-time connectivity, may enhance precision and usability. Transparent reporting of calibration strategies, interference susceptibility, and practical deployment metrics will be essential to inform clinical decision-making and regulatory guidance.

In conclusion, this systematic review and meta-analysis demonstrates that most POC HbA1c devices show acceptable analytical agreement with reference HPLC methods. However, substantial heterogeneity persists, emphasizing the importance of local validation before widespread adoption. Future research should prioritize standardized protocols and real-world implementation studies to enhance reliability and comparability.

Acknowledgements

Not applicable.

Funding

The present study was supported by Shanghai Zhongqiao Vocational and Technical University Research Fund (grant no. 2025ZQZR53). The funding institution had no role in the study design, data collection, analysis, manuscript preparation, or decision to publish.

Availability of data and materials

The data that support the findings of this study, including the extracted data and Stata code, are openly available in the Zenodo repository at https://doi.org/10.5281/zenodo.18014273.

Authors' contributions

YW designed the study, researched data, conducted the analysis and wrote manuscript. MG researched the data, conducted the analysis and contributed to discussion. YR interpreted the data and reviewed the manuscript. ZH researched data, conducted the analysis and critically revised manuscript. YW and ZH confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, an AI tool (ChatGPT, OpenAI) was used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tool as necessary, taking full responsibility for the ultimate content of the present manuscript.

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