# PERFORMANCE OF A MICROFLUIDIC POINT-OF-CARE IMMUNOASSAY FOR D-DIMER COMPARED WITH THE SYSMEX CS-2500 ANALYZER IN THE EXCLUSION OF VENOUS THROMBOEMBOLISM: A COMPARATIVE ANALYSIS

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**Abstract**

**Background:** D-dimer testing is central to venous thromboembolism (VTE) exclusion pathways, but reliance on central laboratory analyzers may delay downstream diagnostic decisions, prolong time to imaging, and defer safe exclusion in patients with low or intermediate clinical pre-test probability.

**Objectives:** To evaluate the analytical agreement and clinical diagnostic performance of a novel microfluidic point-of-care D-dimer assay (mLabs®) against the Sysmex CS-2500 central laboratory analyzer.

**Methods:** In this prospective single-center method-comparison study, 195 paired patient specimens were analyzed using the mLabs® device with 250 µL whole blood and the Sysmex CS-2500 analyzer with 50 µL citrated plasma. For threshold-based categorical comparison, the Sysmex CS-2500 served as the reference method at the 500 ng/mL FEU cutoff. Correlation, agreement, and diagnostic accuracy were assessed using Pearson correlation, intraclass correlation coefficient (ICC), Bland–Altman analysis, and receiver operating characteristic (ROC) analysis, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

**Results:** The mLabs® assay correlated strongly with the reference method (r = 0.94; ICC = 0.96). Sensitivity and specificity at the 500 ng/mL FEU cutoff were 93.4% and 93.0%, respectively; PPV was 97.9%, and NPV was 80.0%; and the area under the ROC curve was 0.986. However, Bland–Altman analysis demonstrated a mean negative bias of −483.5 ng/mL, and 10 Sysmex reference-positive samples were classified as negative by mLabs®. In contrast, 3 Sysmex reference-negative samples were classified as positive.

**Conclusion:** Although the microfluidic point-of-care D-dimer assay (mLabs®) showed strong analytical agreement and excellent overall discrimination, the observed discordant mLabs®-negative/Sysmex-positive results and negative predictive value of 80.0% relative to the reference method indicate that mLabs® should not be assumed to be interchangeable with Sysmex CS-2500 at the 500 ng/mL FEU rule-out threshold. Its most appropriate role is within structured diagnostic algorithms that incorporate clinical pre-test probability.

**Keywords:** D-dimer; point-of-care testing; venous thromboembolism; diagnostic accuracy; microfluidics

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## Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), remains a major global health problem.[1] Because the clinical presentation is often nonspecific, contemporary diagnostic algorithms combine clinical pre-test probability (PTP) with objective testing to guide management.[2,3] In patients with high clinical probability, imaging is generally pursued directly, whereas in patients with low or intermediate PTP, a negative high-sensitivity D-dimer, a fibrin degradation product of cross-linked fibrin, can help exclude VTE and reduce the need for imaging.[2–4] Measurement of D-dimer plays a pivotal role in clinical interpretation. For an assay to be used safely within an exclusion pathway, very high sensitivity and a very high negative predictive value are generally expected.[2,4]

A key limitation of D-dimer testing is reliance on central laboratory analyzers, which may result in turnaround time (TAT) exceeding several hours, delaying downstream diagnostic decisions.[5] In patients with low or intermediate PTP, delayed D-dimer results can postpone the point at which VTE is safely excluded, prolong emergency department or inpatient decision-making, and defer whether additional imaging is needed.[5,6] Point-of-care testing (POCT) addresses this bottleneck by providing rapid results at the patient's bedside, and prior studies have reported substantial reductions in TAT.[5,7] Various D-dimer POCT platforms are commercially available, yet their analytical performance varies, and validation against established laboratory methods remains essential before clinical implementation.[6,7]

A microfluidic fluorescence immunoassay is an antigen–antibody assay performed within small fluidic channels in which small sample volumes are processed inside a cartridge, and the bound immune signal is detected by fluorescence. The mLabs® D-dimer system is a novel microfluidic fluorescence immunoassay designed for rapid, quantitative testing of whole blood or plasma. In contrast, the Sysmex CS-2500 reference platform is a central laboratory analyzer that quantifies D-dimer using an automated particle-enhanced immunoturbidimetric principle.[8] Clarifying the differences between these platforms is clinically relevant because a bedside assay may improve timeliness of care only if threshold-level analytical performance remains reliable enough for safe clinical interpretation. Therefore, this study aimed to assess the analytical agreement and diagnostic accuracy of the mLabs® D-dimer POCT assay compared with the Sysmex CS-2500 for the exclusion of VTE in a clinical hospital cohort, with emphasis on the potential clinical benefits and safety limitations of bedside testing.

## Methods

*Study design and ethical considerations*

This prospective, single-center, method-comparison study was conducted at a tertiary care hospital in Bangkok, Thailand. The study protocol was reviewed and approved by an institutional review board (approval number S025b/64_Exp). The research was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participating subjects prior to sample collection.

*Study population and sample size*

A total of 195 consecutive hospitalized patients in whom central laboratory D-dimer

testing by the Sysmex CS-2500 were clinically indicated as part of routine care were enrolled. Paired research measurements with the mLabs® assay were then performed using whole blood obtained within the same clinical sampling workflow, whereas the reference laboratory assay used citrated plasma. The required sample size was calculated using Buderer's formula[9,10] to achieve sufficient statistical power to estimate diagnostic accuracy. Using anticipated sensitivity and specificity of 96%, a 95% confidence level, and prevalence data from a prospective Thai critical care cohort,[11] the planned minimum sample size was 191. Although the sample size estimation was based on prevalence data from critically ill cohorts, the enrolled participants were not restricted to critically ill patients; they were consecutively recruited from routine hospital admissions undergoing evaluation for suspected VTE. A substantial proportion had comorbid inflammatory or thromboinflammatory conditions, which may elevate D-dimer levels independent of acute VTE.

Inclusion criteria were patients requiring D-dimer measurement as part of their clinical evaluation and for whom a venous blood sample collected in a standard 3.2% sodium citrate tube (nominal draw volume 2.7 mL) was available. Exclusion criteria were gross hemolysis, transfusion within the prior 3 months, or hematocrit < 20%. For threshold-based categorical analysis in this method-comparison study, the Sysmex CS-2500 result served as the reference classification for positive and negative status at the 500 ng/mL FEU cutoff.

*Sample collection and processing*

Venous blood collected in standard 3.2% sodium citrate tubes (nominal draw volume 2.7 mL) was processed within the routine coagulation laboratory workflow. For the reference assay, platelet-poor citrated plasma was prepared, and 50 µL was analyzed on the Sysmex CS-2500. For the index POCT assay, 250 µL of whole blood was applied to the mLabs® cartridge according to the device procedure. Because the two platforms used different specimen matrices, the present comparison reflects platform-specific operation rather than a same-matrix analytical comparison.

*D-dimer assays*

*Index Test: mLabs® D-dimer POCT*

For the index test, 250 µL of whole blood was applied to the disposable mLabs® microfluidic cartridge and analyzed according to the manufacturer's instructions. The manufacturer-specified reportable range for the assay is 50 to 10,000 ng/mL FEU. According to the manufacturer's package insert, the assay is intended for use in conjunction with clinical assessment models to aid in the exclusion of deep vein thrombosis in low- to intermediate-risk patients; the recommended clinical decision cutoff is 500 ng/mL FEU, which was applied in this study.

*Reference method: Sysmex CS-2500*

The reference method for D-dimer measurement was the CS-2500 System (Siemens Healthineers, Germany), a fully automated high-performance coagulation analyzer used in the central laboratory. D-dimer levels were quantified using the INNOVANCE® D-Dimer reagent kit (Siemens Healthineers), an automated particle-enhanced immunoturbidimetric assay.[8] In this study, 50 µL of citrated plasma was analyzed on the system. The assay principle involves agglutination of polystyrene latex particles coated with a highly specific D-dimer monoclonal antibody. When mixed with a plasma sample containing D-dimer, these particles agglutinate, increasing solution turbidity. This change in turbidity is measured photometrically by the analyzer, and the degree of agglutination is directly proportional to the D-dimer concentration. This reference method has been widely evaluated as a high-sensitivity laboratory assay for VTE exclusion when interpreted alongside clinical probability assessment.[8] For interpretive consistency in this study, the conventional clinical decision threshold of 500 ng/mL FEU is also stated for the reference assay when discussing threshold-based clinical interpretation.[3]

*Statistical analysis*

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp). A two-sided *p*-value of less than 0.05 was considered statistically significant.

Before the correlation analysis, paired D-dimer results were graphically inspected for linearity and for potential influential outliers. Pearson's correlation coefficient (r) and linear regression were then used to summarize the linear association between the two continuous methods. Because correlation does not, by itself, establish agreement or interchangeability, the Intraclass Correlation Coefficient (ICC) was additionally calculated using a two-way mixed-effects model with an absolute agreement definition to assess the consistency of measurements across the paired assays.

Agreement between the two methods was further assessed using Bland–Altman analysis. This approach plots the difference between paired measurements against their mean in order to quantify systematic bias between methods. The mean bias was used to estimate the average over- or underestimation by the index assay. In contrast, the 95% limits of agreement (LoA) describe the interval within which most paired differences would be expected to lie.[12] The threshold-based diagnostic performance of the mLabs® assay relative to the Sysmex CS-2500 reference method was evaluated using the manufacturer-recommended clinical decision threshold of 500 ng/mL FEU. A 2×2 contingency table was constructed to calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), along with their corresponding 95% confidence intervals (CIs). To assess agreement between the methods when results were categorized as positive or negative using this cutoff, Cohen's kappa (κ) statistic was calculated. In this analysis, reference-positive and reference-negative categories were defined by the Sysmex CS-2500 result at the same 500 ng/mL FEU cutoff. Finally, to summarize the overall diagnostic performance of the mLabs® assay across all potential thresholds, a Receiver Operating Characteristic (ROC) curve was generated. ROC analysis evaluates how well the assay discriminates between Sysmex reference-positive and reference-negative samples across the full range of possible cutoffs, and the Area Under the Curve (AUC) provides a threshold-independent summary of that discriminatory ability with its 95% CI.

## Results

*Patient characteristics*

A total of 195 patients were enrolled. The overall cohort had a mean age of 61 ± 17 years, and 102/195 patients (52.3%) were male. Based on the Sysmex CS-2500 reference classification at the 500 ng/mL FEU cutoff, 152/195 samples (77.9%) were reference-positive, and 43/195 samples (22.1%) were reference-negative. This high proportion of reference-positive cases reflects the tertiary inpatient referral pattern of this study population. **Table 1** summarizes the actual characteristics of the enrolled cohort, whereas subgroup-specific assay results are presented separately in subsequent tables.

**Table 1.** Baseline characteristics of the enrolled study population (n=195)

| Characteristic | n (%) |
|---|---|
| Age (years), mean ± SD | 61 ± 17 |
| Sex | |
| Male | 102 (52.3) |
| Female | 93 (47.7) |
| Sysmex CS-2500 reference at 500 ng/mL FEU | |
| Positive | 152 (77.9) |
| Negative | 43 (22.1) |

*Correlation and agreement between assays*

The mLabs® assay showed strong correlation with the Sysmex CS-2500 across the analytical range (Pearson's r = 0.94, $p < 0.001$) and excellent reliability, as assessed by intraclass correlation analysis (ICC = 0.96) (**Figure 1**). Bland–Altman analysis demonstrated a mean bias of −483.5 ng/mL, with a lower 95% limit of agreement of −2988 ng/mL and an upper 95% limit of agreement of +2023 ng/mL (**Figure 2**). The negative bias became more pronounced at higher D-dimer concentrations, and visual inspection suggested that divergence between methods began near the clinical decision threshold of 500 ng/mL FEU, which may have contributed to classification discordance around the cutoff. Taken together, these findings indicate that the two assays were strongly associated but were not numerically interchangeable across the full measuring range.

As shown in **Figure 2**, the mean bias was −483.5 ng/mL, with a lower 95% limit of agreement of −2988 ng/mL and an upper 95% limit of agreement of +2023 ng/mL. The solid red line indicates the mean bias, and the black lines represent the lower and upper 95% limits of agreement (±1.96 SD). A proportional negative bias was observed at higher D-dimer concentrations.

*Diagnostic mLabs® D-dimer POCT performance relative to the Sysmex CS-2500 reference method*

Subgroup D-dimer distributions are summarized separately in **Table 2.** Median mLabs® D-dimer values were 2080 [1150–4050] ng/mL FEU in Sysmex reference-positive samples and 310 [220–440] ng/mL FEU in Sysmex reference-negative samples. At the 500 ng/mL FEU cutoff, the positive predictive value (PPV) relative to the reference assay was 97.93% (95% CI: 94.1%–99.6%), while the negative predictive value (NPV) was 80.00% (95% CI: 66.3%–90.0%). Notably, 10 Sysmex reference-positive samples had mLabs® D-dimer values ≤ 500 ng/mL (discordant negative classifications), while 3 Sysmex reference-negative samples had values above the cutoff (discordant positive classifications) (**Table 3**). These findings indicate good overall categorical agreement, but also show clinically relevant discordance around the rule-out threshold.

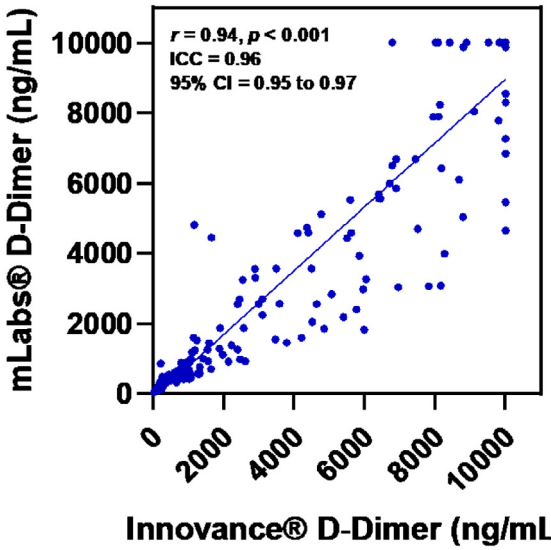



**Figure 1.** Correlation between D-dimer concentrations measured by the Sysmex CS-2500 analyzer and the mLabs® point-of-care testing (POCT) system. Each dot represents an individual sample. The solid line indicates the linear regression fit, and the shaded area represents the 95% confidence interval. A strong positive correlation was observed between the two methods (Pearson's r = 0.94, $p < 0.001$). The conventional clinical decision threshold used in this study was 500 ng/mL FEU.

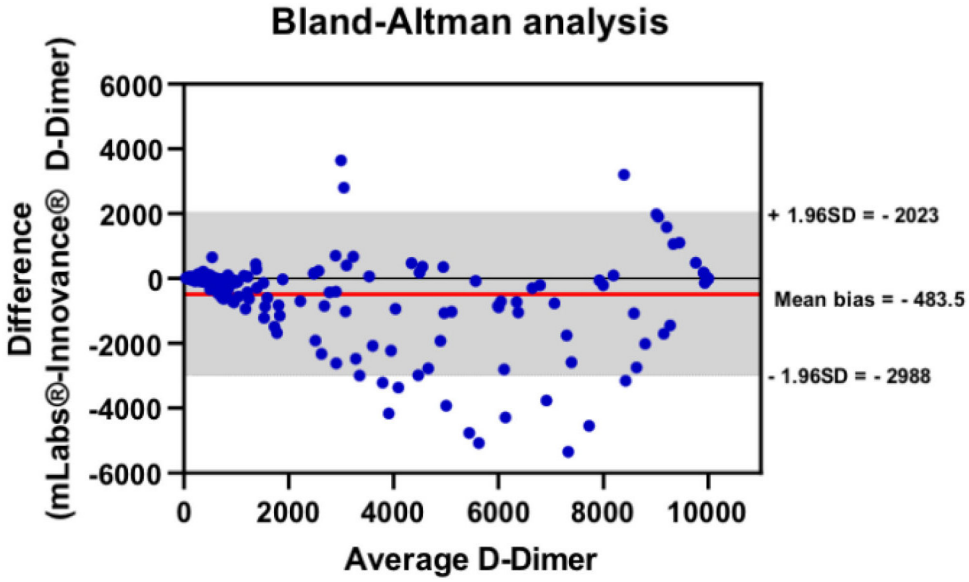



**Figure 2.** Bland–Altman analysis comparing D-dimer concentrations measured by the Sysmex CS-2500 analyzer and the mLabs® POCT system.

**Table 2.** D-dimer distributions by Sysmex CS-2500 reference status for the index and reference assays

| Assay | Sysmex reference-positive (n=152) | Sysmex reference-negative (n=43) |
|---|---|---|
| Sysmex CS-2500, median [IQR], ng/mL FEU | 2550 [1510–4580] | 345 [250–475] |
| mLabs® POCT, median [IQR], ng/mL FEU | 2080 [1150–4050] | 310 [220–440] |

**Table 3.** Diagnostic mLabs® D-dimer POCT performance relative to the Sysmex CS-2500 reference method at the 500 ng/mL FEU cutoff

| mLabs® POCT result | Positive* (n = 152) | Negative* (n = 43) | Total (n = 195) |
|---|---|---|---|
| Positive (>500 ng/mL) | 142 | 3 | 145 |
| Negative (≤500 ng/mL) | 10 | 40 | 50 |
| **Total** | 152 | 43 | 195 |

* Classifications were defined by the Sysmex CS-2500 reference method at the 500 ng/mL FEU cutoff.

Comparison of mLabs® point-of-care testing (POCT) against the Sysmex CS-2500 reference method using the 500 ng/mL fibrinogen equivalent unit (FEU) cutoff. Diagnostic performance: sensitivity = 93.4% (95% CI, 88.3–96.8%); specificity = 93.0% (95% CI, 80.9–98.5%); positive predictive value (PPV) = 97.9% (95% CI, 94.1–99.6%); negative predictive value (NPV) = 80.0% (95% CI, 66.3–90.0%); Cohen's κ = 0.82.

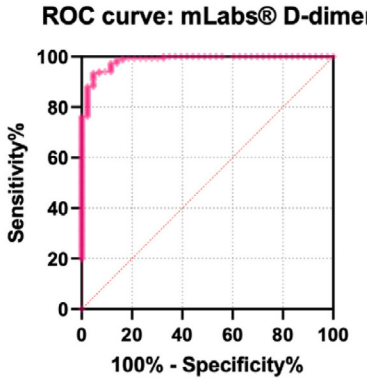
*Descriptive comparison with the Sysmex CS-2500 reference method*

The reference assay also clearly separated the two reference-classified groups at the descriptive level. Median Sysmex CS-2500 D-dimer values were 2550 [1510–4580] ng/mL FEU in Sysmex reference-positive samples and 345 [250–475] ng/mL FEU in Sysmex reference-negative samples, compared with corresponding mLabs®

values of 2080 [1150–4050] and 310 [220–440] ng/mL FEU. Across both subgroups, the Sysmex results were numerically higher than the mLabs® results, consistent with the negative bias observed in the Bland–Altman analysis. Because the Sysmex assay used citrated plasma, whereas the mLabs® platform used whole blood, part of the between-method difference may also reflect matrix-related effects in addition to assay-specific differences. A descriptive assay-level comparison is summarized in **Table 4.**

*Overall diagnostic accuracy*

The overall discriminatory power of the mLabs® D-dimer assay relative to the Sysmex CS-2500 reference classification was assessed using ROC curve analysis (**Figure 3**). The analysis demonstrated outstanding performance, with an Area Under the Curve (AUC) of 0.986 (95% CI, 0.971–0.999; $p < 0.0001$) (**Figure 3**); this indicates excellent separation between reference-positive and reference-negative samples across all possible cutoffs, although threshold-independent discrimination should be interpreted alongside the discordant negative classifications observed at the 500 ng/mL FEU rule-out threshold.




| | |
|---|---|
| AUC | 0.986 |
| *p*-value | < 0.0001 |
| 95% CI | 0.971 to 0.999 |
| Sensitivity (%) | 93.42% |
| Specificity (%) | 93.02% |
| PPV (%) | 97.93% |
| NPV (%) | 80.00% |
| Accuracy (%) | 93.33% |

**Figure 3.** Receiver operating characteristic (ROC) curve for the mLabs® D-dimer assay relative to the Sysmex CS-2500 reference classification. The Area under the curve (AUC) was 0.986 (95% CI, 0.971–0.999; $p < 0.0001$), indicating excellent diagnostic discrimination between reference-positive and reference-negative samples across the full range of thresholds.

**Table 4.** Descriptive comparison of the index and reference D-dimer assays in this study

| Parameter | mLabs® D-dimer POCT (index test) | Sysmex CS-2500 with INNOVANCE® D-Dimer (reference method) |
|---|---|---|
| Analytical principle | Microfluidic fluorescence immunoassay | Automated particle-enhanced immunoturbidimetric assay |
| Specimen/volume evaluated in this study | Whole blood, 250 µL | Citrated platelet-poor plasma, 50 µL |
| Clinical decision threshold referenced in this manuscript | 500 ng/mL FEU | 500 ng/mL FEU |
| Median D-dimer in Sysmex reference-positive samples, ng/mL FEU [IQR] | 2080 [1150–4050] | 2550 [1510–4580] |
| Median D-dimer in Sysmex reference-negative samples, ng/mL FEU [IQR] | 310 [220–440] | 345 [250–475] |
| Observed pattern in this study | Lower values than the reference assay; mean bias −483.5 ng/mL | Numerically higher paired values than the index assay |

## Discussion

This study provides a method-comparison evaluation of the mLabs® microfluidic D-dimer POCT assay against a widely used automated laboratory reference method. The main finding is that strong analytical correlation and excellent ROC-derived discrimination did not translate into complete concordance at the threshold level with the Sysmex CS-2500 reference classification. Specifically, 10 Sysmex-positive samples were classified as negative by mLabs®, and the observed NPV of 80.0% relative to the reference method indicates that a high AUC alone does not establish interchangeability at the clinical decision threshold. In addition, the assay exhibited a negative proportional bias, with increasing underestimation at higher D-dimer concentrations. The descriptive comparison with the Sysmex CS-2500 showed that reference-assay concentrations were numerically higher in both the reference-positive and reference-negative groups, reinforcing the observation that the observed bias was systematic rather than random. These findings help define a more appropriate and clinically cautious role for the device.

The excellent correlation ($r = 0.94$) and reliability (ICC = 0.96) indicate that the mLabs® assay tracked consistently with the reference method across much of its measuring range. However, correlation alone does not establish interchangeability because two methods may change in parallel yet still show clinically important systematic differences at decision-making thresholds.[12] Bland–Altman analysis provided a more informative assessment of agreement and showed a mean negative bias of −483.5 ng/mL, indicating that the mLabs® device tended to report lower values than the CS-2500 System. This pattern is clinically important because D-dimer-based exclusion pathways rely on a binary decision around a low threshold, typically 500 ng/mL FEU. Although categorical agreement was substantial (Cohen's $\kappa = 0.816$), the presence of 10 Sysmex-positive/mLabs-negative discordant results indicates that downward bias near the threshold may alter threshold-based classification. The individual discordant values were not separately tabulated in the original manuscript dataset summary; therefore, we cannot state with precision how tightly they clustered around the cutoff. Nevertheless, visual divergence between methods was evident near 500 ng/mL FEU, and even modest underestimation in this region could reclassify some reference-positive samples as negative. Accordingly, the assay should not be interpreted as interchangeable with the reference method at the rule-out threshold based solely on analytical agreement. At higher D-dimer concentrations, the proportional negative bias may also limit the device's utility for quantitative monitoring in other conditions with markedly elevated D-dimer values, including COVID-19 and inflammatory disease states.[13,14]

Another important finding was an NPV of 80.0% relative to the Sysmex CS-2500 reference classification, indicating incomplete negative agreement at the 500 ng/mL FEU threshold. In this assay-to-assay comparison, predictive values are influenced by the proportion of reference-positive samples, which was high in this cohort (77.9%). However, discordant mLabs-negative/Sysmex-positive cases occurring at or below the clinical cutoff suggest that reduced negative agreement cannot be attributed solely to sample composition; threshold-level classification discordance also contributed. When a rapid POCT result is negative but clinical suspicion remains high, pragmatic safeguards may include reflex confirmatory central-laboratory testing, direct imaging, or embedding the assay within a structured diagnostic algorithm rather than using it in isolation.

The observed sensitivity of 93.4% relative to the Sysmex CS-2500 reference method is high, but it remains slightly below the performance typically expected of assays used for VTE exclusion pathways.[4] The safest interpretation is that the mLabs® device may be useful when embedded within structured diagnostic algorithms that incorporate clinical PTP assessment, rather than as an isolated rule-out tool. This recommendation is supported by contemporary diagnostic pathways, in which D-dimer testing is primarily used in patients with low or intermediate clinical probability and may be combined with validated

high-sensitivity assays, using age-adjusted or probability-adapted thresholds to improve efficiency.[2,3,15] In the present study, however, such threshold modification was not validated for the mLabs® platform and therefore cannot yet be recommended for clinical implementation. Broadly, the analytical performance observed here is within the range reported for other rapid D-dimer platforms, although direct comparisons across studies should be made carefully because of differences in sample matrices, clinical populations, and reference standards.[16,17] This emphasis on method-comparison rather than correlation alone is consistent with other Thai POCT evaluation work in different analytes, specifically a hemoglobin/anemia POCT method-comparison study, which similarly showed that clinically relevant bias may persist despite strong correlation and good overall discrimination.[18]

Several limitations should be acknowledged. First, this was a single-center study conducted in a tertiary inpatient cohort with a high proportion of Sysmex reference-positive samples, limiting generalizability to low-prevalence outpatient rule-out settings. Second, the assays were performed on different specimen matrices: the mLabs® platform used 250 µL whole blood, whereas the Sysmex CS-2500 used 50 µL citrated platelet-poor plasma. Although this reflects real-world platform use, matrix-related differences—including hematocrit effects, cellular components, and cartridge flow behavior—may influence threshold-level performance and may have contributed to part of the observed between-method bias.[17] Third, the study was powered for diagnostic accuracy estimation but was not specifically designed to establish definitive NPV performance in low-prevalence populations or to validate age-adjusted cutoffs for this platform. Finally, turnaround time, operational workflow, and cost-effectiveness were not formally evaluated.

## Conclusion

The mLabs® D-dimer POCT system demonstrated strong analytical agreement and excellent ROC-derived discrimination when compared with the Sysmex CS-2500 central laboratory reference method. Nevertheless, because of the observed discordant mLabs-negative/Sysmex-positive results, negative bias around the clinical threshold, and an NPV of 80.0% relative to the reference method, the microfluidic point-of-care D-dimer assay (mLabs®) should not be assumed to be interchangeable with the Sysmex CS-2500 at the 500 ng/mL FEU cutoff. Its most appropriate clinical role is as a component of structured diagnostic pathways that incorporate validated clinical pre-test probability assessment. Users should also be aware that the assay tends to underestimate D-dimer at higher concentrations, which may limit its utility for quantitative monitoring in other disease states. Future multicenter studies in lower-prevalence outpatient populations, ideally including whole-blood testing and workflow outcomes, are warranted.

## Conflict of Interest

The authors declare no competing financial or non-financial interests in relation to the work described.

## Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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