Multicenter Performance Evaluation of a New D-dimer Assay for the Quantitative Determination of D-dimer.

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Introduction and Aim

D-dimer is a global indicator of coagulation activation and fibrinolysis, and is thus an indirect marker of thrombotic activity.[1] The major diagnostic application of D-dimer testing lies in the exclusion of thromboembolic events, such as deep vein thrombosis (DVT) or pulmonary embolism (PE).[1] D-dimer can also be used to support diagnosis and monitoring of hypercoagulable states such as disseminated intravascular coagulopathy (DIC).[1-3]

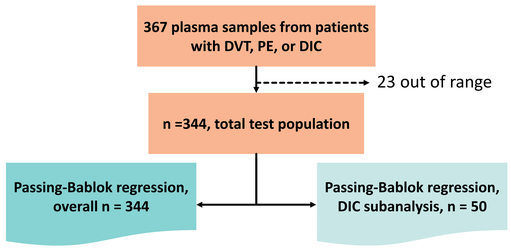
The aim of this multicenter study was to evaluate the performance of the new INNOVANCE D-Dimer 2.0 assay on the automated CS-5100 coagulation analyzer, both from Siemens Healthineers.

Methods

Assay principle

- Turbidimetric quantitation following polystyrene particle aggregation in the presence of D-dimer detected.
- Measuring interval: 0.190 to 7.500 mg/L Fibrinogen Equivalent Units (FEU), extended to 80.000 mg/L FEU by autodilution.

Method comparison of the INNOVANCE D-Dimer 2.0 assay vs. INNOVANCE D-Dimer assay (per CLSI EPO9c)[4]



- Four study sites: one in Germany, three in the US.
- Statistical Evaluation: Nonparametric regression (Passing-Bablok) and parametric correlation measure (Pearson) for the total sample population and the sub-population of DIC.

Adult reference Interval and healthy pediatric population correspondence (per CLSI EP28-A3c)[4]

- Apparently healthy adult donors (≥ 18 years of age), n =153 samples (US population).
- Statistical Evaluation: 2.5th to 97.5th as well as 90th percentiles using the nonparametric method.
- In addition, comparison of apparently healthy pediatric subjects (≥ 10 to < 18 years of age), n = 24 (US population) to adult reference interval.

Reproducibility (per CLSI EP05-A3c)[4]

- Plasma pools and control material (n = 8) covering the measuring interval (3x5x2x3 design).
- Statistical Evaluation: Precision estimates using a three-factor nested analysis of variance (ANOVA).

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Results

Method Comparison

In total, 344 plasma samples were included in the Passing-Bablok regression: The INNOVANCE D-Dimer 2.0 assay demonstrated high comparability with the INNOVANCE D-Dimer assay within the overall population, as well as for the sub-population of patients with suspicion of or known DIC. Negligible bias was observed at the validated clinical cut-off (0.500 mg/L FEU).

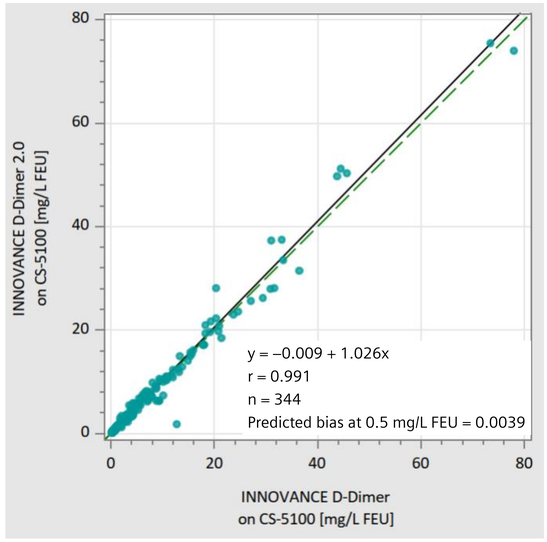

Figure 1. Comparison of the INNOVANCE D-Dimer 2.0 assay vs INNOVANCE D-Dimer assay for the total population.

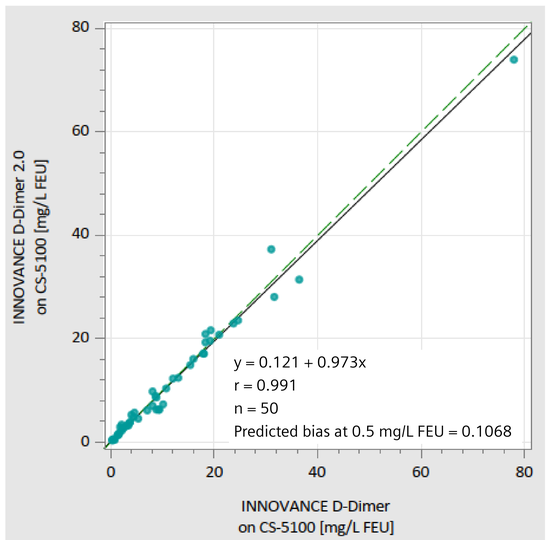

Figure 2. Comparison of the INNOVANCE D-Dimer 2.0 assay vs INNOVANCE D-Dimer assay for the DIC sub-population.

Table 1. Descriptive statistics for the method comparison of INNOVANCE D-Dimer 2.0 assay to the INNOVANCE D-Dimer assay on the CS-5100 analyzer.

Samples	N	Slope	Intercept [mg/L FEU]	Predicted Bias at 0.5 mg/L FEU	Pearson Correlation Coefficient (r)
Overall	344	1.026	–0.009	0.0039	0.991
DIC only	50	0.973	0.121	0.1068	0.991

Adult reference Interval and healthy, pediatric population correspondence

The adult two-sided reference interval (2.5th to 97.5th percentile) as well as the 90th percentile was calculated. In the pediatric evaluation, 24 valid samples ranged from <0.190 to 0.974 mg/L FEU. Among these, 23 fell within the reference interval established for adults.

Table 2. Descriptive Statistics for Reference Interval calculation. All units are mg/L FEU.

Population	N	Minimum	2.5th %ile	Median	90th %tile	97.5th %ile	Maximum
Adult	153	<0.190	<0.190	<0.190	0.468	0.942	1.522

Reproducibility

Reproducibility testing confirmed robust precision with CVs ≤4.39% throughout the measuring interval.

Table 3. The coefficients of variation (CVs) results of the reproducibility study (all sites combined) for the INNOVANCE D-Dimer 2.0 assay on CS-5100 System.

Sample	n	Mean [mg/L FEU]	CV [%] Repeatability (within-run)	Between-Run	Between-Day	Between-Site	Total (combined sites)
Plasma Sample 1	90	0.2539	2.54	1.49	1.91	2.63	4.39
DDi2Ctl1[a]	90	0.3413	2.01	0.00	1.93	2.32	3.62
Plasma Sample 2	90	0.5665	1.58	0.87	1.84	0.92	2.74
DDi2Ctl2[b]	90	0.7366	0.92	0.93	2.09	2.03	3.19
DDi2Ctl3[c]	90	3.0235	1.27	1.02	2.19	1.31	3.03
Plasma Sample 3	90	6.4584	1.65	1.63	2.93	2.11	4.30
Plasma Sample 4	90	25.8025	0.96	0.92	2.14	3.07	3.97
Plasma Sample 5	90	61.8035	1.02	1.04	2.12	3.20	4.11

a. INNOVANCE D-Dimer 2.0 assay Control 1; b. INNOVANCE D-Dimer 2.0 assay Control 2; c. INNOVANCE D-Dimer 2.0 assay Control 3

Conclusion

The INNOVANCE D-Dimer 2.0 assay shows excellent agreement when compared to its predecessor, the INNOVANCE D-Dimer assay, in this multicenter method comparison. Furthermore, the new assay showed robust reproducibility under real-world conditions. Pediatric samples fit well within a newly established reference interval for adults. These results confirm the suitability of the new liquid, ready-to-use assay for routine quantitative determination of D-dimer.

References

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3. Suzuki K, et al. A re-evaluation of the D-dimer cut-off value for making a diagnosis according to the ISTH overt-DIC diagnostic criteria: communication from the SSC of the ISTH. J Thromb Haemost. 2018;16:1442-4.
4. All CLSI Guidelines can be found on the CLSI website: https://clsi.org

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