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Global Siemens Headquarters

Siemens AG
Wittelsbacherplatz 2
80333 Muenchen
Germany

Global Siemens Healthcare Headquarters

Siemens AG
Healthcare Sector
Henkestrasse 127
91052 Erlangen
Germany
Telephone: +49 9131 84 - 0
www.siemens.com/healthcare

Global Division

Siemens Healthcare Diagnostics Inc.
511 Benedict Avenue
Tarrytown, NY 10591-5005
USA
www.siemens.com/diagnostics

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Comparison of the Siemens IMMULITE 2000 Anti-CCP IgG Assay with the Axis-Shield DIASTAT Anti-CCP Assay: A Clinical Evaluation

Conarpe C[1], Woods A[2], Goldblatt J[1], Samson L[3], Bitcon V[1], Geier M[4], Tan S[1], Fan J[1], Martel J[1]

[1]Siemens Healthcare Diagnostics Inc., Tarrytown, NY, U.S.; [2]Siemens Healthcare Diagnostics Inc., Berkeley, CA, U.S.; [3]Siemens Healthcare Diagnostics sas, Saint Denis, France; [4]Siemens Healthcare Diagnostics Inc., Los Angeles, CA, U.S.

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Summary

This multicenter clinical trial evaluated the performance of the IMMULITE® 2000 Anti-CCP IgG assay* (Siemens Healthcare Diagnostics) for reproducibility and clinical equivalence to the Axis-Shield Diagnostics DIASTAT Anti-CCP assay. The IMMULITE 2000 assay demonstrated high reproducibility; for samples with mean index values of 1.78 to 139.39, within-run CVs were 10.8% to 3.9% and total within-device CVs were 13.1% to 4.9%, respectively. Results of the method comparison showed good initial concordance between the IMMULITE 2000 assay and the DIASTAT assay, with a positive agreement of 89.8%, a negative agreement of 98.9%, and a total agreement of 95.7%. The clinical specificity for the IMMULITE 2000 and DIASTAT assays was high: 97.5% and 97.0%, respectively. The clinical sensitivity of these assays was lower—58.9% and 63.8%, respectively—but consistent with the performance of commercial anti-CCP assays. ROC analysis demonstrated no significant difference between the two assays, and further testing of a subset of samples with the Abbott ARCHITECT Anti-CCP assay and the Phadia ImmunoCAP 250 EliA CCP assay yielded similar clinical performance results. With the RA prevalence at 52.2%, the positive and negative predictive values of the IMMULITE 2000 assay were 96.3% and 68.5%, respectively; and those of the DIASTAT assay were 95.8% and 71.1%, respectively. Thus, the IMMULITE 2000 Anti-CCP IgG assay exhibited performance equivalent to that of the DIASTAT assay in the clinical setting.

*Not available in the U.S.

Introduction

Three sites participated in this multicenter clinical trial to evaluate the reproducibility of the IMMULITE 2000 Anti-CCP IgG assay and to compare its performance with that of the Axis-Shield Diagnostics DIASTAT Anti-CCP assay for detecting anti-CCP antibodies in clinical samples.

The diagnosis of rheumatoid arthritis (RA) depends mainly on clinical signs, with support from laboratory testing and imaging. The 2010 Rheumatoid Arthritis Classification Criteria, developed jointly by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), embody a scoring system that assigns point values to clinical signs and laboratory test results. These laboratory tests include either rheumatoid factor (RF) or anti–citrullinated protein antibody (ACPA) assays, the latter also known as anti–cyclic citrullinated peptide (anti-CCP) assays.[1]

The sensitivity and specificity of RF assays are moderate, at 69% and 85%, respectively.[2] Anti-CCP assays offer sensitivity at least comparable to that of RF assays in RA but with higher specificity.[3–5] Various studies report anti-CCP assay sensitivities of 41% to 92%[2,5–11] and specificities of 88% to 100%.[2,5,8–12] Assay performance, however, varies with the test population. In a review by Riedemann et al., anti-CCP assay sensitivities in well-established RA ranged from 64.4% to 96%, but in early RA from 14.4% to 83.5%.[7] When RF and anti-CCP assay results are both positive, the specificity for RA approaches 100 percent.[13]

Table 1 lists several factors affecting the diagnostic accuracy of anti-CCP antibody assays.

Table 1. Factors affecting serological detection of anti-CCP antibodies in RA.

Factor	Comments
Disease stage / severity	Lower sensitivity is associated with early RA or undifferentiated arthritis. In early disease, patient anti-CCP may be undetectable. Some patients are initially anti-CCP negative but develop anti-CCP later in the disease.[7,14]
Treatment	A small percentage of treated RA patients may become anti-CCP negative.[14]
Patient haplotype	Individuals who carry one or more copies of the so-called "shared epitope" allele are much more likely to have anti-CCP–positive RA than those who do not. Not all RA patients produce anti-CCP.[15]
Viral infection	Certain viral infections (EBV, HCV, PvB19) may account for cross-reactivity in anti-CCP assays and lead to false-positive results,[6] thereby reducing specificity.
Assay antigens	In a method comparison of 11 manufacturers' anti-CCP assays performed on the same population, the choice of antigens used in the assays was reportedly the single most important cause of differences in assay sensitivity.[6]
Assay cutoff	The manufacturer's choice of a cutoff level balances sensitivity against specificity.

Sensitivity and specificity are not the only measures for assessing the performance and utility of an anti-CCP assay: the positive predictive value (PPV) and negative predictive value (NPV), which depend on the pretest probability (disease prevalence), are equally important.

Materials and Methods

Assay Principles

IMMULITE 2000 Assay. The Siemens IMMULITE 2000 Anti-CCP IgG assay is intended for the in vitro semiquantitative determination of IgG autoantibodies specific to cyclic citrullinated peptide (CCP) in human serum or plasma. The assay is a two-cycle, sequential chemiluminescent immunometric assay. In the first reaction cycle, the patient sample (10 µL, prediluted) is incubated with a biotinylated CCP–coated bead for 30 minutes. A wash step removes unbound nonspecific antibodies. During the second reaction cycle, reagent containing anti–human IgG conjugated to alkaline phosphatase is added and incubated for 30 minutes. After washing to remove excess conjugate, the chemiluminescent substrate is added and incubated for 5 minutes. The assay provides a result expressed as reactive or nonreactive relative to a 4.0 U/mL cutoff.

Axis-Shield Diagnostics DIASTAT Assay. The assay is a semiquantitative/qualitative ELISA in which patient anti-CCP IgG antibodies bind to microtiter wells coated with a highly purified synthetic cyclic citrullinated peptide. Enzyme-labeled monoclonal anti–human IgG antibody then binds captured patient antibodies. After addition of a substrate followed by a stop solution, the amount of bound conjugate is determined by comparing the absorbance to that of a reference control (for the qualitative procedure) or to that of a standard curve (for the semiquantitative procedure). In this study, absorbance ratio (patient absorbance / mean reference control absorbance) results of >5 U/mL were considered positive.

Abbott ARCHITECT Assay. The assay is a semiquantitative chemiluminescent microparticle immunoassay in which patient anti-CCP IgG antibodies bind to CCP-coated paramagnetic microparticles. Acridinium ester–labeled anti–human IgG antibody binds captured patient antibodies. After the addition of pretrigger and trigger solutions, the instrument measures the resulting chemiluminescent emission, which is directly related to the anti-CCP IgG concentration in the patient sample. Results of >5 U/mL were considered positive.

Phadia ImmunoCAP 250 EliA Assay. The assay is a fluoroenzyme immunoassay in which patient anti-CCP IgG antibodies bind to citrullinated synthetic peptide–coated wells and are bound in turn by enzyme-labeled anti–human IgG antibodies. After addition of a development solution followed by a stop solution, the instrument reads the fluorescent response, which is directly related to the anti-CCP IgG concentration in the patient sample. Results are reported in lot-specific EliA units, where a negative result is <7 U/mL; an equivocal result, 7–10 U/mL; and a positive result, >10 U/mL.

Reproducibility Testing Procedure

Reproducibility testing was performed at three sites over 10 days, two runs per day, with four replicates per run for all sample pools and control materials.

Method Comparison Procedure

A method comparison study evaluated the IMMULITE 2000 Anti-CCP IgG assay performance against that of the Axis-Shield DIASTAT Anti-CCP assay. For the IMMULITE 2000 testing, all samples were tested with one of two assay reagent lots but not both. Samples were analyzed on both systems on the same day and/or within the same freeze–thaw cycle.

A total of 1515 samples were analyzed: 791 from patients clinically diagnosed with RA, the diagnosis having been made by a board-certified rheumatologist or internist whenever possible; 464 from patients clinically diagnosed without RA but diagnosed with potentially cross-reactive infections or clinical conditions (whose samples thus had the potential to cross-react in anti-CCP assays and produce false-positive results); and 260 from apparently healthy subjects. Samples from osteoarthritis, systemic lupus erythematosus, and psoriatic arthritis patients accounted for 47.6% of the non-RA samples. For the sensitivity and specificity analyses, unless otherwise stated, the data were split into two cohorts: RA and non-RA, the latter consisting of the non-RA disease state samples and the apparently healthy samples.

Additionally, a subset of samples (n = 559) were retested to compare the IMMULITE 2000 system against the ARCHITECT system and the ImmunoCAP 250 system. The latter two systems' performance relative to RA diagnosis was also evaluated.

Results

Reproducibility Results

Total within-device CVs of results for six samples with mean index values ranging from 1.78 to 139.39 (n = 472 and 484, respectively) were 13.1% and 4.9%, respectively. Per CLSI EP5-A2,[16] total within-device imprecision consists of within-run, run-to-run, and day-to-day variation.

Method Comparison Results

The cutoffs used for the method comparisons were as follows:

- Siemens IMMULITE 2000 assay: nonreactive, <4.0 U/mL; reactive, ≥4.0 U/mL
- Axis-Shield DIASTAT assay: negative, <5.0 U/mL; positive, ≥5.0 U/mL
- Abbott ARCHITECT assay: negative, <5.0 U/mL; positive, ≥5.0 U/mL
- Phadia ImmunoCAP 250 EliA assay: negative, <7 U/mL; equivocal, 7–10 U/mL; positive, >10 U/mL.

Table 2 gives the method comparison results for the IMMULITE 2000 assay vs. the Axis-Shield DIASTAT assay. The positive and negative percent agreements were 89.8% and 98.9%, respectively, with an overall agreement of 95.7%.

Table 2. Method comparison: IMMULITE 2000 assay vs. DIASTAT assay.

		Axis-Shield DIASTAT		
		Positive	Negative	Totals
IMMULITE 2000	Reactive	473	11	484
	Nonreactive	54	977	1031
	Totals	527	988	1515

	Percent Agreement	95% LCL	95% UCL
Positive	89.8	86.8	92.2
Negative	98.9	98.0	99.4
Total	95.7	94.6	96.7

LCL = lower confidence limit; UCL = upper confidence limit

Tables 3 and 4 show the performance of the IMMULITE 2000 and DIASTAT assays vs. RA diagnosis. The clinical sensitivity of the IMMULITE 2000 assay was 58.9% (466/791), with a 95% confidence interval (CI) of 55.4% to 62.4%; the clinical specificity was 97.5% (706/724), with a 95% CI of 96.1% to 98.5%.The clinical sensitivity of the DIASTAT assay was 63.8% (505/791), with a 95% confidence interval (CI) of 60.4% to 67.2%; the clinical specificity was 97.0% (702/724), with a 95% CI of 95.4% to 98.1%.

Table 3. Method comparison: IMMULITE 2000 assay vs. RA diagnosis.

		RA Diagnosis		
		RA	Non-RA	Totals
IMMULITE 2000	Reactive	466	18	484
	Nonreactive	325	706	1031
	Totals	791	724	1515

	Percent Agreement	95% LCL	95% UCL
Sensitivity	58.9	55.4	62.4
Specificity	97.5	96.1	98.5

Table 4. Method comparison: DIASTAT assay vs. RA diagnosis.

		RA Diagnosis		
		RA	Non-RA	Totals
Axis Shield DIASTAT	Reactive	505	22	527
	Nonreactive	286	702	988
	Totals	791	724	1515

	Percent	95% LCL	95% UCL
Sensitivity	63.8	60.4	67.2
Specificity	97.0	95.4	98.1

An ROC analysis of the IMMULITE 2000 and Axis-Shield DIASTAT assays vs. RA diagnosis is shown in Figure 1 and Table 5. The analysis indicates that the two assays are not statistically different ($P = 0.0915$).

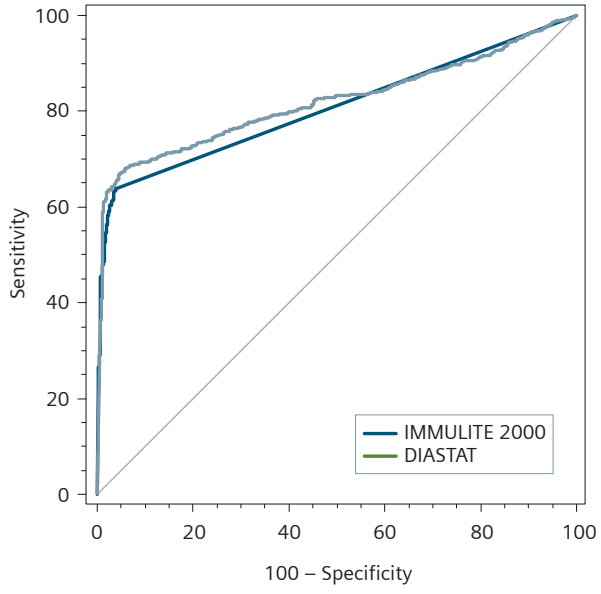

Figure 1. ROC analysis: IMMULITE 2000 assay vs. Axis-Shield DIASTAT assay.

Table 5. ROC analysis statistics.

	AUC	SE	95% CI
IMMULITE 2000	0.806	0.00914	0.785 to 0.826
DIASTAT	0.820	0.0114	0.800 to 0.839

IMMULITE 2000 vs. DIASTAT	
Difference between areas	0.0138
Standard error	0.00816
95% Confidence interval	–0.00222 to 0.0298
z Statistic	1.688
Significance level	$P = 0.0915$

Tables 6 and 7 show IMMULITE 2000 assay results vs. RA diagnosis divided into early RA (diagnosed ≤2 years prior) and well-established RA (diagnosed >2 years prior). Sensitivities for the IMMULITE 2000 assay were 43.6% for early RA and 64.2% for well-established RA. Sensitivities for the DIASTAT assay were 49.0% for early RA and 69.0% for well-established RA.

Table 6. Method comparison: IMMULITE 2000 assay vs. RA diagnosis. RA samples are divided into early and well-established. (See text for definition.)

		RA Diagnosis		
		Early RA	Well-Est. RA	Totals
IMMULITE 2000	Reactive	89	377	466
	Nonreactive	115	210	325
	Totals	204	587	791

	Sensitivity	95% LCL	95% UCL
Early RA	43.6	36.7	50.7
Well-Est. RA	64.2	60.2	68.1

Table 7. Method comparison: DIASTAT assay vs. RA diagnosis. RA samples are divided into early and well-established.

		RA Diagnosis		
		Early RA	Well-Est. RA	Totals
DIASTAT	Reactive	100	405	505
	Nonreactive	104	182	286
	Totals	204	587	791

	Sensitivity	95% LCL	95% UCL
Early RA	49.0	42.0	56.1
Well-Est. RA	69.0	65.1	72.7

Comparisons between the two assays by patient category—RA, non-RA, and apparently healthy—are summarized in Tables 8–10. The highest percent agreements were those for RA patients, with positive and negative agreements of 91.5% and 98.6%, respectively. Lower positive agreements (50%) were observed for non-RA patients and healthy subjects, with negative agreements remaining high at about 99%.

Table 8. Method comparison: IMMULITE 2000 assay vs. Axis-Shield assay, RA only.

		Axis-Shield DIASTAT		
		Positive	Negative	Totals
IMMULITE 2000	Reactive	462	4	466
	Nonreactive	43	282	325
	Totals	505	286	791

	Percent Agreement	95% LCL	95% UCL
Positive	91.5	88.7	93.8
Negative	98.6	96.5	99.6
Total	94.1	92.2	95.6

Table 9. Method comparison: IMMULITE 2000 assay vs. Axis-Shield assay, non-RA only.

		Axis-Shield DIASTAT		
		Positive	Negative	Totals
IMMULITE 2000	Reactive	9	5	14
	Nonreactive	9	441	450
	Totals	18	446	464

	Percent Agreement	95% LCL	95% UCL
Positive	50.0	26.0	74.0
Negative	98.9	97.4	99.6
Total	97.0	95.0	98.3

Table 10. Method comparison: IMMULITE 2000 assay vs. Axis-Shield assay, apparently healthy only.

		Axis-Shield DIASTAT		
		Positive	Negative	Totals
IMMULITE 2000	Reactive	2	2	4
	Nonreactive	2	254	256
	Totals	4	256	260

	Percent Agreement	95% LCL	95% UCL
Positive	50.0	6.8	93.2
Negative	99.2	97.2	99.9
Total	98.5	96.1	99.6

The positive predictive value (true positives / test-reported positives) and negative predictive value (true negatives / test-reported negatives) were also calculated for the IMMULITE 2000 and DIASTAT assays. The IMMULITE 2000 assay's PPV and NPV were 96.3% and 68.5%, respectively; and those of the DIASTAT assay were 95.8% and 71.1%, respectively (Table 11). In this study, the RA prevalence was 52.2%.

Table 11. Positive and negative predictive values of the IMMULITE 2000 and DIASTAT assays at an RA prevalence of 52.2%.

Assay	Statistic	True Results	Assay Results	Percent Value	LCL	UCL
IMMULITE 2000	PPV	466	484	96.3%	94.2%	97.8%
	NPV	706	1031	68.5%	65.5%	71.3%
DIASTAT	PPV	505	527	95.8%	93.7%	97.4%
	NPV	702	988	71.1%	68.1%	73.9%

PPV = positive predictive value; NPV = negative predictive value

In the additional method comparison performed on a subset of samples (n = 559) the ARCHITECT and ImmunoCAP 250 assays were each compared to the IMMULITE 2000 assay and to RA diagnosis (Tables 12 and 13). Performance characteristics of the ARCHITECT and ImmunoCAP 250 assays were similar to those obtained in the comparison between the IMMULITE 2000 and DIASTAT assays.

Table 12. Additional method comparison on 559 samples: ARCHITECT assay vs. IMMULITE 2000 assay and vs. RA diagnosis.

		ARCHITECT		
		Positive	Negative	Totals
IMMULITE 2000	Reactive	159	6	165
	Nonreactive	23	371	394
	Totals	182	377	559

	Percent Agreement	95% LCL	95% UCL
Positive	87.4	81.6	91.8
Negative	98.4	96.6	99.4
Total	94.8	92.6	96.5

	Percent	95% LCL	95% UCL
Sensitivity	65.5	59.5	71.2
Specificity	97.6	95.1	99.0
Total	82.3	78.9	85.4

Table 13. Additional method comparison on 559 samples: ImmunoCAP 250 assay vs. IMMULITE 2000 assay and vs. RA diagnosis.

		ImmunoCAP 250			
		Positive	Negative	Equiv	Total
IMMULITE 2000	Reactive	159	6	0	165
	Nonreactive	16	376	2	394
	Totals	175	382	2	559

	Percent Agreement	95% LCL	95% UCL
Positive	90.9	85.6	94.7
Negative	98.4	96.6	99.4
Total	96.1	94.1	97.5

	Percent	95% LCL	95% UCL
Sensitivity	64.5	58.4	70.3
Specificity	98.6	96.5	99.6
Total	82.4	79.0	85.5

Discussion

This study demonstrated good performance of the IMMULITE 2000 Anti-CCP IgG assay for the characteristics evaluated: reproducibility; and positive, negative, and total agreement compared to the Axis-Shield DIASTAT assay. The IMMULITE 2000 assay showed good specificity (97.5%) and sensitivity (58.9%, Table 3) consistent with those reported for anti-CCP assays.

On the basis of all clinical information available, 791 samples were collected from patients diagnosed with RA. Of these samples, 466 were positive for anti-CCP by the IMMULITE 2000 assay (Table 3). This assay's sensitivity was not significantly different from that of the Axis-Shield DIASTAT assay for all samples (63.8%, Table 4), as demonstrated by ROC analysis (Figure 1 and Table 5). Moreover, the positive, negative, and total agreement obtained by comparing IMMULITE 2000 and DIASTAT assay results on RA samples alone were 91.5%, 98.6%, and 94.1%, respectively (Table 8). Finally, the IMMULITE 2000 and DIASTAT assays' sensitivities were similar to those of the Abbott ARCHITECT assay (65.5%, Table 12) and the Phadia ImmunoCAP 250 assay (64.5%, Table 13) on a subset of the samples (n = 559).

The sensitivity of anti-CCP assays varies widely with the population selected for testing (Table 1), dropping to as low as 14.4% in early RA.[17] Accordingly, in the present study, sensitivities varied with time following diagnosis, showing a difference between early and well-established RA of 20 percentage points: 43.6% and 64.2% for the IMMULITE 2000 assay, and 49.0% and 69.0% for the DIASTAT assay.

Anti-CCP assays are not considered sensitive enough for RA screening.[7] The greater value of anti-CCP tests lies in their high specificity: a positive anti-CCP assay test correlates strongly with the presence of RA. Moreover, the specificity and positive predictive value for RA approach 100% when anti-CCP and RF results are both positive.[12,13]

Finally, the IMMULITE 2000 and DIASTAT assays showed comparable positive and negative predictive values, assay metrics that are just as important as sensitivity and specificity. In the population tested in this study, which had an RA prevalence of 52.2%, the IMMULITE 2000 PPV and NPV were 96.3% and 68.5%, respectively; and those of the DIASTAT assay were 95.8% and 71.1%, respectively.

The IMMULITE 2000 assay demonstrated high specificity with acceptable sensitivity, and a high positive predictive value. These metrics were comparable to those of the other manufacturers' assays used in this study.

Conclusions

The IMMULITE 2000 Anti-CCP IgG assay demonstrated good reproducibility, as well as performance comparable to that of the Axis-Shield DIASTAT assay (and two other manufacturers' assays on a subset of the samples) in terms of agreement, clinical sensitivity, and clinical specificity. Thus, the IMMULITE 2000 assay exhibited performance characteristics consistent with those of commercially available assays for the detection of anti-CCP IgG antibodies in clinically significant populations.

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