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External Clinical Verification of the Atellica CI High-Sensitivity Troponin I Assay

A. Bonito, N.K. Padda, M. Anostario, H. Zhang, R. Fonstad
Siemens Healthcare Diagnostics Inc., Tarrytown, NY, U.S.

Background

High-sensitivity cardiac troponin assays are guideline recommended for the diagnosis of acute coronary syndrome (ACS).[1,2] Previously, a high-sensitivity troponin I (TnIH) assay was developed and commercialized for use on the Atellica IM Analyzer: Atellica IM TnIH assay.[3] Recently, the Atellica CI Analyzer (Figure 1) was added to the Atellica Solution portfolio, with a reduced footprint of 1.9 square meters. The Atellica CI Analyzer is an integrated clinical chemistry and immunoassay analyzer designed for low-to-mid volume laboratories and features the same reagents, consumables, and sophisticated user interface as the Atellica IM and CH Analyzers.[4]

Objective

To verify the reproducibility and clinical concordance performance characteristics of the Atellica IM TnIH assay on the Atellica CI and Atellica IM Analyzers.

Material and Methods

Reproducibility

The reproducibility study consisted of 3 sites (2 external, 1 internal), 5 days, 2 runs per day, 2 hours apart, and 3 replicates/run per CSLI EP05-A3. Eight reproducibility panels (4 Medical Decision Pools, 1 serum pool, 3 lithium heparin plasma pools), and 3 controls levels were tested on 1 reagent lot at 3 sites.

Figure 1. The Atellica CI Analyzer

Clinical Performance

- Clinical performance was determined by testing patient samples from a clinical study of emergency department patients presenting with signs and symptoms of ACS at 29 sites across the US. Sites were selected from different regions of the United States to capture the demographic and geographic diversity of the intended use population. Inclusion criteria were the following: informed consent to participate in the study; adult, >22 years of age; presentation with signs or symptoms suspicious for a possible ACS event. Exclusion criteria: inability to meet all inclusion criteria. A total of 2677 subjects were enrolled, and 2461 available subject samples were tested. Each subject provided blood specimens for up to 5 time points and using 2 collection tube types (serum and lithium heparin plasma) at each time point.
- Samples were collected at baseline, ≥0.5–1.5, ≥1.5–4, ≥4–9, and ≥9–24 hr. Samples were split among three sites and assayed in singlicate on both Atellica CI and Atellica IM Analyzers.
- The Atellica IM TnIH assay clinical concordance study was performed on both Atellica CI and Atellica IM Analyzers using the 99th percentile upper reference limit (URL) determined on the Atellica IM Analyzer. Clinical concordance was calculated between the 99th percentile URL and the adjudicated diagnosis of myocardial infarction at each time point.
- The following assessments were conducted for serum and lithium heparin plasma samples:
  - All patients using a single overall 99th percentile URL cut-off value.
  - Each gender subgroup using gender-specific cut-offs and presented separately per gender
  - Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).
- Comparison of clinical performance was performed with available results tested on both systems (n=2455).

Results

The following results are representative of the performance of the assay.

Reproducibility results of the Atellica IM TnIH assay on the Atellica CI Analyzer and the Atellica IM Analyzer are shown in Table 1.

Table 1. Reproducibility of the Atellica IM TnIH Assay on the Atellica CI Analyzer and the Atellica IM Analyzer.

Assay: TnIH	Atellica CI Analyzer			Atellica IM Analyzer			Atellica CI Analyzer vs Atellica IM
Sample	Mean pg/mL (ng/L)	SD [LCI – UCI]* pg/mL (ng/L)	%CV [LCI–UCI]	Mean pg/mL (ng/L)	SD [LCI–UCI] pg/mL (ng/L)	%CV [LCI–UCI]	SD Ratio [LCI–UCI]
Control 1	117.41	3.17 [2.42–4.60]	2.7 [2.1–3.9]	122.43	5.38 [3.64–10.27]	4.4 [3.0–8.4]	0.59 [0.30–1.01]
Control 2	6556.60	128.03 [108.74–155.71]	2.0 [1.7–2.4]	6641.12	189.31 [123.13–404.84]	2.9 [1.9–6.1]	0.68 [0.31–1.09]
Control 3	21911.62	487.87 [352.96–789.55]	2.2 [1.6–3.6]	22274.84	671.64 [397.69–2029.19]	3.0 [1.8–9.1]	0.73 [0.23–1.47]
L1	31.56	0.99 [0.70–1.65]	3.1 [2.2–5.2]	32.13	0.98 [0.67–1.85]	3.1 [2.1–5.8]	1.01 [0.50–1.90]
L2	60.24	2.00 [1.40–3.51]	3.3 [2.3–5.8]	60.76	1.95 [1.23–4.59]	3.2 [2.0–7.5]	1.03 [0.41–2.09]
L3	15560.46	522.09 [313.06–1495.07]	3.4 [2.0–9.6]	15646.77	430.19 [271.83–1010.89]	2.7 [1.7–6.5]	1.21 [0.46–3.69]
S1	8.19	0.64 [0.41–1.50]	7.9 [5.0–18.3]	8.11	0.42 [0.32–0.62]	5.2 [4.0–7.6]	1.53 [0.85–3.66]
S2	32.88	1.57 [0.90–5.52]	4.8 [2.7–16.8]	32.12	1.31 [0.84–2.96]	4.1 [2.6–9.2]	1.20 [0.46–4.36]
S3	122.00	5.17 [3.30–11.73]	4.2 [2.7–9.6]	119.19	4.78 [2.91–12.91]	4.0 [2.4–10.8]	1.08 [0.38–2.74]
S4	1428.74	57.33 [34.36–164.52]	4.0 [2.4–11.5]	1387.40	51.24 [30.11–160.11]	3.7 [2.2–11.5]	1.12 [0.34–3.49]
S5	23361.95	647.34 [400.90–1633.75]	2.8 [1.7–7.0]	23531.55	678.16 [407.59–1923.40]	2.9 [1.7–8.2]	0.95 [0.31–2.65]

**LCI: Lower limit of 95% confidence interval, UCI: Upper limit of 95% confidence interval. S1-5: serum; L1-3: lithium heparin*

Reproducibility coefficients of variation (CVs) for the Atellica CI Analyzer were 2.0–7.9% at 8.19–23361.95 pg/mL (ng/L) and Atellica IM Analyzer, 2.7–5.2% at 8.11–23531.55 pg/mL (ng/L). The Atellica CI vs IM Analyzer SD Ratio (95% Confidence Interval [CI]) ranged from 0.59 (0.30, 1.01) to 1.53 (0.85, 3.66) for reproducibility samples demonstrating that the Atellica CI Analyzer was statistically equivalent or better compared to the Atellica IM Analyzer across all sample levels tested. Note: The reproducibility testing was performed as a 5-day study. The repeatability and within-lab precision results from this study are not intended as a verification of the repeatability and within-lab precision performance goals (verified using 20-day verification studies elsewhere).

Table 2. Demographic information for subjects included in the analyses.

	Overall (n=2461)
Age (yr.)	
Mean (SD)	56.8 (12.9)
Median [Min, Max]	56.0 [23.0, 93.0]
Race (n, %)	
White	1383 (56.2%)
Black	978 (39.7%)
Asian	24 (1.0%)
Hawaiian	3 (0.1%)
American Indian	14 (0.6%)
Multiple Races	19 (0.8%)
Other	40 (1.6%)
Gender (n, %)	
Female	1067 (43.4%)
Male	1394 (56.6%)

Clinical Performance

Comparison of the clinical performance of the Atellica CI Analyzer and the Atellica IM Analyzer is shown in the following tables. Results presented in Tables 3 through 6 are for lithium heparin samples. Results for serum samples were similar.

The Atellica TnIH Clinical Concordance study was performed on both the Atellica CI and the Atellica IM Analyzers using the 99th percentile determined on the Atellica IM Analyzer. Due to the limited availability of some aliquots, not all samples have results on both systems. A total of 2461 samples were tested on the Atellica CI Analyzer and 2455 were tested on the Atellica IM Analyzer. A comparison of clinical performance was done with available results tested on both systems (N=2455).

Table 3. Sensitivity for Atellica CI Analyzer vs Atellica IM Analyzer.

URL	Timepoint	Atellica CI Analyzer			Atellica IM Analyzer			Difference (CI–IM)	
		n	Estimate	95% CI	n	Estimate	95% CI	Diff	95% CI
Overall 99th percentile (pooled gender)	Baseline	286	85.3%	80.7–88.9	286	85.3%	80.7–88.9	0.0%	-5.8–5.8
	≥ 0.5–1.5 hr	256	90.2%	86.0–93.3	256	90.2%	86.0–93.3	0.0%	-5.2–5.2
	≥ 1.5–4 hr	251	92.8%	89.0–95.4	251	93.2%	89.4–95.7	-0.4%	-5.0–4.2
	≥ 4–9 hr	244	93.9%	90.1–96.2	244	94.3%	90.6–96.6	-0.4%	-4.8–4.0
	≥ 9–24 hr	221	92.8%	88.6–95.5	221	92.8%	88.6–95.5	0.0%	-5.0–5.0
Female 99th percentile	Baseline	98	87.8%	79.8–92.9	98	87.8%	79.8–92.9	0.0%	-9.4–9.4
	≥ 0.5–1.5 hr	88	89.8%	81.7–94.5	88	89.8%	81.7–94.5	0.0%	-9.4–9.4
	≥ 1.5–4 hr	84	96.4%	90.0–98.8	84	96.4%	90.0–98.8	0.0%	-6.8–6.8
	≥ 4–9 hr	84	95.2%	88.4–98.1	84	95.2%	88.4–98.1	0.0%	-7.4–7.4
	≥ 9–24 hr	77	93.5%	85.7–97.2	77	93.5%	85.7–97.2	0.0%	-8.6–8.6
Male 99th percentile	Baseline	188	83.0%	77.0–87.7	188	83.5%	77.5–88.1	-0.5%	-8.1–7.1
	≥ 0.5–1.5 hr	168	88.1%	82.3–92.2	168	89.3%	83.7–93.1	-1.2%	-8.1–5.7
	≥ 1.5–4 hr	167	89.8%	84.3–93.5	167	89.2%	83.6–93.1	0.6%	-6.1–7.3
	≥ 4–9 hr	160	91.3%	85.8–94.7	160	90.6%	85.1–94.2	0.6%	-5.9–7.1
	≥ 9–24 hr	144	91.7%	86.0–95.2	144	91.0%	85.2–94.6	0.7%	-6.1–7.5

Overall 99th percentile URL (pooled gender): 45.20 pg/mL (ng/L); Female 99th percentile URL: 34.11 pg/mL (ng/L); Male 99th percentile URL: 53.48 pg/mL (ng/L).

Table 4. Specificity for Atellica CI Analyzer vs Atellica IM Analyzer.

URL	Timepoint	Atellica CI Analyzer			Atellica IM Analyzer			Difference (CI–IM)	
		n	Estimate	95% CI	n	Estimate	95% CI	Diff	95% CI
Overall 99th percentile (pooled gender)	Baseline	1836	91.1%	89.7–92.3	1836	91.0%	89.6–92.2	0.1%	-1.8–1.9
	≥ 0.5–1.5 hr	1768	90.7%	89.3–92.0	1768	90.6%	89.1–91.8	0.2%	-1.8–2.1
	≥ 1.5–4 hr	1609	89.7%	88.1–91.1	1609	89.5%	87.9–90.9	0.2%	-1.9–2.3
	≥ 4–9 hr	1046	86.9%	84.7–88.8	1046	86.7%	84.5–88.6	0.2%	-2.7–3.1
	≥ 9–24 hr	847	86.0%	83.4–88.1	847	85.8%	83.3–88.0	0.1%	-3.2–3.4
Female 99th percentile	Baseline	826	91.9%	89.8–93.6	826	91.5%	89.4–93.2	0.4%	-2.3–3.0
	≥ 0.5–1.5 hr	795	90.4%	88.2–92.3	795	90.7%	88.5–92.5	-0.3%	-3.1–2.6
	≥ 1.5–4 hr	705	89.9%	87.5–91.9	705	89.6%	87.2–91.7	0.3%	-2.9–3.5
	≥ 4–9 hr	440	87.7%	84.3–90.5	440	87.7%	84.3–90.5	0.0%	-4.4–4.4
	≥ 9–24 hr	338	84.9%	80.7–88.3	338	84.6%	80.4–88.1	0.3%	-5.1–5.7
Male 99th percentile	Baseline	1010	91.0%	89.1–92.6	1010	90.9%	89.0–92.5	0.1%	-2.4–2.6
	≥ 0.5–1.5 hr	973	91.1%	89.1–92.7	973	90.8%	88.8–92.4	0.3%	-2.3–2.9
	≥ 1.5–4 hr	904	89.7%	87.6–91.5	904	89.8%	87.7–91.6	-0.1%	-2.9–2.7
	≥ 4–9 hr	606	87.5%	84.6–89.9	606	87.3%	84.4–89.7	0.2%	-3.6–3.9
	≥ 9–24 hr	509	87.4%	84.3–90.0	509	86.8%	83.6–89.5	0.6%	-3.5–4.7

Table 5. PPV for Atellica CI Analyzer vs Atellica IM Analyzer.

URL	Timepoint	Atellica CI Analyzer			Atellica IM Analyzer			Difference (CI–IM)	
		n	Estimate	95% CI	n	Estimate	95% CI	Diff	95% CI
Overall 99th percentile (pooled gender)	Baseline	408	59.8%	55.0–64.4	409	59.7%	54.8–64.3	0.1%	-6.6–6.8
	≥ 0.5–1.5 hr	395	58.5%	53.6–63.2	398	58.0%	53.1–62.8	0.4%	-6.4–7.3
	≥ 1.5–4 hr	399	58.4%	53.5–63.1	403	58.1%	53.2–62.8	0.3%	-6.5–7.1
	≥ 4–9 hr	366	62.6%	57.5–67.4	369	62.3%	57.3–67.1	0.2%	-6.7–7.2
	≥ 9–24 hr	324	63.3%	57.9–68.3	325	63.1%	57.7–68.1	0.2%	-7.2–7.6
Female 99th percentile	Baseline	153	56.2%	48.3–63.8	156	55.1%	47.3–62.7	1.1%	-9.9–12.0
	≥ 0.5–1.5 hr	155	51.0%	43.2–58.7	153	51.6%	43.8–59.4	-0.7%	-11.7–10.4
	≥ 1.5–4 hr	152	53.3%	45.4–61.0	154	52.6%	44.7–60.3	0.7%	-10.4–11.7
	≥ 4–9 hr	134	59.7%	51.2–67.6	134	59.7%	51.2–67.6	0.0%	-11.6–11.6
	≥ 9–24 hr	123	58.5%	49.7–66.9	124	58.1%	49.3–66.4	0.5%	-11.7–12.6
Male 99th percentile	Baseline	247	63.2%	57.0–68.9	249	63.1%	56.9–68.8	0.1%	-8.3–8.5
	≥ 0.5–1.5 hr	235	63.0%	56.6–68.9	240	62.5%	56.2–68.4	0.5%	-8.2–9.1
	≥ 1.5–4 hr	243	61.7%	55.5–67.6	241	61.8%	55.6–67.7	-0.1%	-8.7–8.5
	≥ 4–9 hr	222	65.8%	59.3–71.7	222	65.3%	58.8–71.3	0.5%	-8.3–9.2
	≥ 9–24 hr	196	67.3%	60.5–73.5	198	66.2%	59.3–72.4	1.2%	-8.1–10.4

Table 6. NPV for Atellica CI Analyzer vs Atellica IM Analyzer.

URL	Timepoint	Atellica CI Analyzer			Atellica IM Analyzer			Difference (CI–IM)	
		n	Estimate	95% CI	n	Estimate	95% CI	Diff	95% CI
Overall 99th percentile (pooled gender)	Baseline	1714	97.5%	96.7–98.2	1713	97.5%	96.7–98.2	0.0%	-1.1–1.1
	≥ 0.5–1.5 hr	1629	98.5%	97.7–99.0	1626	98.5%	97.7–99.0	0.0%	-0.9–0.9
	≥ 1.5–4 hr	1461	98.8%	98.1–99.2	1457	98.8%	98.1–99.3	-0.1%	-0.9–0.8
	≥ 4–9 hr	924	98.4%	97.3–99.0	921	98.5%	97.5–99.1	-0.1%	-1.3–1.1
	≥ 9–24 hr	744	97.8%	96.5–98.7	743	97.8%	96.5–98.7	0.0%	-1.5–1.6
Female 99th percentile	Baseline	771	98.4%	97.3–99.1	768	98.4%	97.3–99.1	0.0%	-1.3–1.3
	≥ 0.5–1.5 hr	728	98.8%	97.7–99.3	730	98.8%	97.7–99.4	0.0%	-1.2–1.2
	≥ 1.5–4 hr	637	99.5%	98.6–99.8	635	99.5%	98.6–99.8	0.0%	-1.0–1.0
	≥ 4–9 hr	390	99.0%	97.4–99.6	390	99.0%	97.4–99.6	0.0%	-1.7–1.7
	≥ 9–24 hr	292	98.3%	96.1–99.3	291	98.3%	96.0–99.3	0.0%	-2.4–2.5
Male 99th percentile	Baseline	951	96.6%	95.3–97.6	949	96.7%	95.4–97.7	-0.1%	-1.7–1.6
	≥ 0.5–1.5 hr	906	97.8%	96.6–98.6	901	98.0%	96.9–98.7	-0.2%	-1.6–1.2
	≥ 1.5–4 hr	828	97.9%	96.7–98.7	830	97.8%	96.6–98.6	0.1%	-1.3–1.6
	≥ 4–9 hr	544	97.4%	95.7–98.5	544	97.2%	95.5–98.3	0.2%	-1.8–2.2
	≥ 9–24 hr	457	97.4%	95.5–98.5	455	97.1%	95.2–98.3	0.2%	-2.0–2.5

Clinical concordance testing comparing the Atellica CI and IM Analyzers demonstrated that assay sensitivity, specificity, PPV, and NPV (overall, female, male) are nearly indistinguishable between the systems, as determined by the 95%CI of the percent differences. This was demonstrated using Newcombe's approach in which the 95%CI encompassed a difference of zero.

Conclusion

The SD ratio analyses showed that the Atellica CI Analyzer was statistically equivalent to the Atellica IM Analyzer across all reproducibility sample levels tested. The Atellica CI and IM Analyzers demonstrated equivalent clinical performance in terms of sensitivity, specificity, NPV and PPV.

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