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ORIGINAL INVESTIGATION

Multicenter evaluation of a fully automated third-generation anti-HCV antibody screening test with excellent sensitivity and specificity

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Abstract Early detection of hepatitis C virus (HCV) is an important step in preventing progression to cirrhosis and hepatocellular carcinoma. Serologic assays for anti-hepatitis C (anti-HCV) antibody are valuable first-line tests in the screening and diagnosis of HCV infection. The aim of this multicenter study was to compare the Elecsys® Anti-HCV assay with alternative CE-marked Anti-HCV antibody assays against a range of samples that included 1,138 blood donors, 3,553 unselected routine daily specimens, and 46 pre-selected seroconversion panels. Specificity of the Elecsys Anti-HCV assay was 99.5% with blood donor samples and 99.4% with routine clinical specimens. These were similar to those obtained with the Prism® Anti-HCV, Architect® Anti-HCV assay, ADVIA® Centaur Anti-HCV assay and Vitros® Eci aHCV assays. Seroconversion sensitivity for the Elecsys Anti-HCV assay was similar to that of the Architect Anti-HCV, AxSYM HCV version 3.0, ADVIA Centaur Anti-HCV, and Vitros Eci aHCV assays. In fact, seroconversion testing on 46 commercially available panels showed that the difference in first detecting a positive blood sample was less than one day between assays (not statistically significant). The Elecsys Anti-HCV assay as well as the Architect, Prism, and Vitros Anti-HCV immunoassays revealed a seroconversion sensitivity of 100%, whereas the ADVIA Centaur HCV immunoassay showed a sensitivity of only 97.5% (39/40). Overall, the performance of the Elecsys Anti-HCV assay was similar to the performances of the comparator CE-marked Anti-HCV antibody assays.

Keywords Hepatitis C virus · Anti-HCV antibody screening · Elecsys Anti-HCV · Architect Anti-HCV · ADVIA Centaur Anti-HCV · Vitros Eci aHCV

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Introduction

The hepatitis C virus (HCV) was discovered in 1989 [1] and identified as the major causative agent of non-A, non-B hepatitis. The virus is 50–60 nm in size and its genome consists of single-stranded ribonucleic acid (RNA; 9.300 nucleotides) [2]. Estimates suggest that up to 3% of the world's population, between 130 and 170 million people, are infected with HCV [3], with the highest prevalence of HCV infection being found in the African and the Eastern Mediterranean regions.

Transmission of HCV is mainly by parenteral routes, such as intravenous drug abuse, contaminated medical equipment, and tattoos. Although cases of sexual and

perinatal transmission of HCV have been reported, it is considered less common than parenteral transmission [4]. Estimates vary, but between 50 and 85% of HCV-infected individuals go on to develop a persistent infection [3], and of these, around 25% will ultimately suffer from cirrhosis and a significant proportion will go on to develop hepatocellular carcinoma [5].

Many patients infected with HCV are asymptomatic making clinical diagnosis difficult. Consequently, screening assays play an essential role in the diagnostic process [6]. In clinical practice, the usual approach is to test for antibodies to HCV (anti-HCV), which indicates that the individual has been infected with the virus, and then to detect HCV RNA to confirm that it is an active infection [7]. Indirect serologic tests are comparatively easy to perform and cheaper than direct tests; consequently, they are widely used as first-line assessments in screening and diagnosis. Quantitative measurement of HCV RNA using the reverse transcriptase polymerase chain reaction (RT–PCR) is mainly used for therapeutic decision-making and the assessment of treatment response [8, 9]. In addition to the role of serologic testing as part of clinical diagnosis, the screening of blood donors for anti-HCV has been responsible for a substantial decrease in the risk of acquiring HCV infection from blood transfusions. Given the importance of early detection of infection in routine clinical practice and blood donors, there is a need for specific, sensitive, reliable, and rapid assays for the detection of all major HCV genotypes.

The present multicenter study was designed to compare the performance of the Elecsys® Anti-HCV assay (Roche Diagnostics, Penzberg, Germany), a diagnostic assay for the qualitative detection of antibodies against HCV in human serum or plasma, with alternative CE-marked Anti-HCV antibody assays. Further objectives were to collect the comparative data required for CE marking and to generate sensitivity and specificity data based on well-characterized samples.

Materials and methods

Study design

Six centers (Allgemeines Krankenhaus Linz, Linz, Austria; Medizinisches Versorgungszentrum Futurebiolab, Munich, Germany; Gemeinschaftspraxis für Laboratoriumsmedizin, Mikrobiologie und Humangenetik, Mönchengladbach, Germany; Blutzentrale des Roten Kreuzes Oberösterreich, Linz, Austria; Ospedale di Dolo, Dolo, Italy; Ospedale Santa Maria degli Angeli, Servizio Trasfusionale, Pordenone, Italy) involved in the hepatitis diagnosis and screening participated in the study. Using a special panel of preselected samples together with blood donor samples and unselected routine samples, the centers compared the performance of the Elecsys Anti-HCV assay with that of the ADVIA® Centaur Anti-HCV assay (Siemens Medical Solutions Diagnostics, Bad Nauheim, Germany), the Vitros® Eci aHCV assay (Ortho Clinical Diagnostics, Neckargemuend, Germany), the Architect® Anti-HCV assay (Abbott Diagnostics, Wiesbaden, Germany), the Prism® Anti-HCV assay (Abbott Diagnostics, Wiesbaden, Germany) or the AxSYM® HCV version 3.0 assay (Abbott Diagnostics, Wiesbaden, Germany). With respect to the Elecsys Anti-HCV assay, all participating centers underwent a process of system and reagent familiarization that included assessment of intra-assay precision before the formal start of the study. Each center tested its own samples; the samples were not exchanged between laboratories.

Serum samples

Samples for serologic testing included fresh sera from 1,138 blood donors (Linz center) and 3,553 routine clinical specimens (Munich, Mönchengladbach, and Dolo centers). Fresh samples were stored for 24 h at 4–8°C. A further 46 commercially available seroconversion samples (a series of sequential follow-up samples) were also tested. These included panels PHV 901, 904–906, 908, 909–921 (SeraCare Life Sciences, Milford, MA, USA) and panels 6212–6216, 6224–6229, 9041, 9044–9047, 9054, 9055, 9058, 10017, 10026, 10039, 10041, 10057, 10058, 10062, 10071, 10165, and 10185 (ZeptoMetrix Corp, Buffalo, NY, USA). Seroconversion panels were stored at −20°C.

Serological assays

The Elecsys Anti-HCV assay is a two-step sandwich electrochemiluminescence immunoassay that is intended for use with the MODULAR Analytics® E170 and Cobas e immunoassay analyzers. In the first step, 40 µl of sample is incubated for 9 min with 60 µl of reagent 1 (biotinylated recombinant HCV antigens derived from core regions, NS3 and NS4) and 60 µl of reagent 2 (HCV antigens labeled with a ruthenium complex). These labeled antigens form a sandwich complex with IgG and IgM anti-HCV antibodies in the sample. The second 9-minute incubation starts with the addition of 40 µl of streptavidin-coated microparticles, which bind the antibody–antigen sandwich complex to the solid phase via the interaction between streptavidin and biotin in the sandwich complex. The reaction mixture is then aspirated into the measuring cell, where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are removed with a system buffer, flushing out excess reagent and sample (ProCell). Application of a voltage to the electrode then induces ruthenium chemiluminescence, which is measured by a

Table 1 Technical specifications of the Elecsys Anti-HCV assay and comparator assays

	Test format	Antigens	Time to result (mins)	Sample type	Sample volume (µl)
Elecsys Anti-HCV	1-step sandwich	Core, NS3, NS4	20	Serum, plasma (heparin, EDTA, citrate)	40
Architect Anti-HCV	2-step sandwich	HCr-43, c-100-3-SOD	28	Serum, plasma (heparin, EDTA, citrate, oxalate)	20
ADVIA Centaur Anti-HCV	2-wash sandwich	C200, c22-3, NS5	41	Serum, plasma (heparin, EDTA)	10
Vitros Eci-a HCV	2-step sandwich	C22-3, c200, NS5	55	Serum, plasma (heparin, EDTA, citrate)	20
Prism Anti-HCV	2-step sandwich	C100-3, HCr43, NS5		Serum, plasma (EDTA, oxalate, citrate	50
AxSym Anti-HCV	2-step sandwich	HCr43, c200, c100-3, NS5	30	Serum, plasma (heparin, EDTA, citrate, oxalate	33

photomultiplier. The results are determined automatically by the analyzer software. The electrochemiluminescence signal obtained from the sample is compared with the cutoff value obtained previously from assay calibration.

Comparator assays were performed and repeated in accordance with standard laboratory procedures. Table 1 summarizes and compares the technical specification of the assays included in the study.

In the current study, serum samples with a signal/cutoff ratio <0.9 were considered negative and those ≥1.0 as positive, with those between 0.9 and <1.0 considered indeterminate. Initially reactive (IR) specimens were retested at least once (RR) and twice if sufficient material was available (RR/RR). Reference confirmatory assays, all of which were CE-marked and represented state-of-the-art screening assays, were performed on repeatedly discrepant samples and consistently positive samples.

For blood donor samples, confirmatory testing consisted of an HCV-RNA PCR (Roche Diagnostics Cobas Amplipprep/Amplicor HCV qual or Roche Diagnostics Cobas Ampliscreen HCV v 2.0) followed by HCV immunoblot (Biorad DECISCAB HCV PLUS Assay, Innogenetics Inno-LIA HCV Score, Mikrogen recomblot HCV IgG 2.0, Chiron RIBA 3.0 SIA [retesting only]) if discrepant results were obtained for the screening assay and HCV PCR. HCV immunoblot was used as the confirmatory assay for routine samples.

Discrepancy resolution

Inconclusive or indeterminate results were indicated in the discrepancy sheets. Inconclusives and indeterminates were excluded from the specificity calculations unless a proven anamnestic patient's history proved HCV infection.

Statistical analysis

The performance of the Elecsys Anti-HCV assay was compared with the comparator assays using the Kruskall–Wallis test. No significant difference between performances of the two assays was indicated by overlapping lower 95% confidence intervals. The Wilcoxon test was used to compare the seroconversion sensitivity of different anti-HCV assays. A P value <0.05 was considered statistically significant.

Results

Blood donor samples

The Elecsys Anti-HCV assay demonstrated similar, but slightly lower specificity to the Prism Anti-HCV assay with tests conducted on blood donor samples at the Linz center (Table 2). Of the 1,138 samples, 18 yielded an IR or RR result with the Elecsys Anti-HCV assay, of which 15 tested

Table 2 Specificity of the Elecsys Anti-HCV and Prism Anti-HCV antibody assays with blood donor samples (Linz center)

	Elecsys Anti-HCV	Prism Anti-HCV
Number of specimens	1,138	1,138
IR ≥1 s/co	8	2
IR ≥0.9 s/co– <1.0 s/co	2	n.a.
RR ≥1 s/co	7	2
RR ≥0.9 s/co– <1.0 s/co	1	n.a.
HCV blot confirmed positive	0	0
HCV blot 'indeterminate'*	1*	0
Specificity % IR ≥1 s/co	99.38	99.83
Specificity % IR incl. ≥0.9 s/co	99.21	n.a.
Specificity % RR ≥1 s/co	99.47	99.83
Specificity % RR incl. ≥0.9 s/co	99.38	n.a.
Lower confidence limit (95%; two-sided) (RR ≥1) %	98.85–99.81	99.37–99.98

n.a. not available

* One sample with 'indeterminate' HCV blot was excluded from the specificity calculation

negative subsequently on HCV immunoblot and one gave an 'indeterminate' result.

Routine samples

Similar specificity was seen when the Elecsys Anti-HCV assay was compared with the Architect Anti-HCV assay (Munich), ADVIA Centaur HCV assay (Mönchengladbach), and Vitros Eci aHCV assay (Dolo) for testing routine clinical samples (Table 3). An unusually high number of 'indeterminates' occurred with the Biorad DECISCAB HCV PLUS assay during confirmatory tests at the Dolo center. Retesting these samples with the Chiron RIBA 3.0 SIA resulted in seven samples remaining 'indeterminate', four becoming reactive, and four negative. Because the number of 'indeterminates' affected both assays in the same way, assay specificity was unaffected. Notably, the Elecsys Anti-HCV assay revealed a sensitivity of 100%, whereas the ADVIA Centaur HCV assay missed one immunoblot-confirmed reactive sample resulting in a sensitivity of 97.5%.

Table 4 provides a summary of results. For blood donors, 10 samples were initially reactive (≥9 s/co) with eight being repeatedly reactive. Similarly, for routine samples, 117 samples were initially reactive with 112 being repeatedly reactive. Overall, the Elecsys Anti-HCV assay demonstrated excellent specificity with respect to both blood donor samples (99.5%) and unselected routine clinical samples (99.4%). Statistical analysis using the Kruskall–Wallis test showed that there were no statistical differences between any of the anti-HCV assays with respect to seroconversion sensitivity (Table 4).

Seroconversion panels

The Elecsys Anti-HCV assay demonstrated similar sensitivity to the other anti-HCV antibody assays with respect to early detection of HCV. Using HCV-RNA PCR (the most sensitive assay) as a reference, there was little difference overall between the assays with regard to the mean number of days before a first positive test was recorded (Table 5). Comparisons between the Elecsys Anti-HCV assay and ADVIA Centaur Anti-HCV assay showed identical times for 34/46 (74%) panels with five (11%) and seven (15%) panels detected earlier and later, respectively. Comparisons with the Vitros Eci aHCV assay showed identical times for 31/45 (69%) panels with five (11%) and nine (20%) panels detected earlier and later, respectively. Comparisons between the Elecsys Anti-HCV assay and the Architect Anti-HCV assay showed identical times for 32/46 (70%) panels, while three (6%) panels were detected earlier and 11 (24%) panels were detected later. Of the 37 panels tested with the AxSYM HCV version 3.0 assay, identical timings were seen in 27/37 (73%) panels, while six (16%) and four (11%) panels were detected earlier and later, respectively, with the Elecsys Anti-HCV assay.

Table 3 Specificity of the Elecsys Anti-HCV and Architect Anti-HCV antibody assays with unselected routine blood samples

	Munich center		Mönchengladbach center		Dolo center	
	Elecsys	Architect	Elecsys	ADVIA Centaur	Elecsys	Vitros Eci
Number of specimens	1,300	1,300	1,208	1,208	1,045	1,045
IR ≥1 s/co	24	19	47	41	44	48
IR ≥0.9 s/co– <1.0 s/co	2	n.a.	0	n.a.	0	1
RR ≥1 s/co	25	20	43*	41	43	48
RR ≥0.9 s/co– <1.0 s/co	0	n.a.	0	n.a.	1	1
HCV blot confirmed positive	15	15	40	39**	19	19
HCV blot 'indeterminate'*	2 IR/1 RR[a]	1[a]	1***	0	13[c]	15[c]
Specificity % IR ≥1 s/co	99.45	99.69	99.49	99.83	98.81	98.62
Specificity % IR incl. ≥0.9 s/co	99.30	n.a.	99.49	n.a.	98.81	98.52
Specificity % RR ≥1 s/co	99.30[b]	99.69	99.83*	99.83	98.91	98.62
Specificity % RR incl. ≥0.9 s/co	99.30[b]	n.a.	99.83*	n.a.	98.81	98.52
Lower confidence limit (95%; two-sided) (RR ≥1) %	98.67–99.98	99.20–99.91	99.38–99.98*	99.38–99.98	98.06–99.46	97.69–99.24

* One sample IR positive (s/co 218.2) but insufficient quantity for retesting. The sample was set to RR positive

** One sample IR/RR negative in Centaur, immunoblot confirmed positive, i.e. Centaur RR false negative

*** One sample with 'indeterminate' HCV blot was excluded from the specificity calculation

[a] One Elecsys sample and two Architect samples with 'indeterminate' HCV blot were excluded from the specificity calculation

[b] Sample 494, 1058 IR borderline, RR positive

[c] Thirteen Elecsys samples and 15 Vitros Eci samples with 'indeterminate' HCV blot were excluded from the specificity calculation

Table 4 Summary of Elecsys Anti-HCV results on blood donor samples (Linz center) and unselected routine specimens (Munich, Munchengladbach and Dolo centers)

	Elecsys Anti-HCV Blood donors	Elecsys Anti-HCV Routine samples
Number of specimens	1,138	3,553
IR ≥1 s/co	8	115
IR ≥0.9 s/co– <1.0 s/co	2	2
RR ≥1 s/co	7	111
RR ≥0.9 s/co– <1.0 s/co	1	1
HCV blot confirmed positive	0	74
HCV blot 'indeterminate'*	1*	16 IR/15 RR*
Specificity % IR ≥1 s/co	99.38	99.28
Specificity % IR incl. ≥0.9 s/co	99.21	99.2
Specificity % RR ≥1 s/co	99.47	99.36
Specificity % RR incl. ≥0.9 s/co	99.38	99.34
Lower confidence limit (95%; two sided) (RR ≥1) %	98.85–99.81	99.04–99.60

* One blood donor sample and 16 routine samples with 'indeterminate' HCV blot were excluded from the specificity calculation

The Wilcoxon test demonstrated that there was no significant difference between seroconversion sensitivity between any of the assays with $P > 0.2$ for all comparisons (Table 5). In direct comparison with PCR, the assays showed significant differences with P values < 0.0001 (Wilcoxon test) (Table 6).

Discussion

Molecular amplification of HCV RNA in blood samples by PCR is the most sensitive indicator of acute infection with HCV. However, serologic tests for the detection of HCV antibodies are also important first-line tests in screening and diagnosis of HCV infection. The presence of the Anti-HCV antibody in serum and plasma reflects exposure to the virus and may indicate an acute, chronic, or resolved infection [10]. Moreover, as chronic HCV infection can result in silent progression to cirrhosis and hepatocellular carcinoma, early anti-HCV antibody detection is an important first step in the management of chronic hepatitis C [6].

Today, a number of commercial Anti-HCV antibody assays are available for routine screening and diagnosis. These include the Elecsys Anti-HCV assay, which is the most rapid of all tests included in this study with a time to result of 20 min. As the present study has demonstrated, it also provides sensitivity and specificity that is as good as, if not better than, other established CE-marked Anti-HCV antibody assays. Based on an analysis of more than 4,600

Table 5 Seroconversion sensitivity testing

Seroconversion panel	First positive blood sample (day)				
	Elecsys	ADVIA centaur	Vitros Eci	Architect	AxSym
PHV901	32	32	n.t.	32	n.t
PHV904	7	9	9	9	9
PHV905	11	14	14	14	14
PHV906	0	0	0	0	0
PHV908	11	11	19	11	11
PHV909	31	28	28	28	31
PHV910	8	8	8	8	8
PHV911	14	14	14	14	14
PHV912	0	7	7	7	7
PHV913	7	7	7	7	10
PHV914	16	16	16	16	19
PHV915	12	5	12	12	5
PHV916	19	16	19	16	n.t.
PHV917	72	72	72	72	72
PHV918	27	27	24	24	24
PHV920	13	13	7	13	13
PHV921	14	4	4	7	7
6212	12	12	12	12	12
6213	26	26	26	26	n.t.
6214	30	30	30	25	25
6215	20	20	20	20	20
6216	1	0	0	0	n.t.
6224	19	19	19	19	19
6225	33	33	33	33	35
6226	37	37	37	37	37
6227	32	32	32	32	n.t.
6228	28	31	28	28	28
6229	17	17	17	17	17
9041	38	38	38	38	38
9044	21	21	21	21	21
9045	37	37	37	37	37
9046	0	0	0	0	0
9047	28	28	28	28	28
9054	9	8	3	3	8
9055	35	34	34	34	35
9058	10	10	10	7	n.t.
10017	34	34	33	33	n.t.
10026	27	27	27	26	27
10039	26	26	23	26	n.t.
10041	6	6	6	6	n.t.
10057	0	0	0	0	0
10058	0	0	0	0	0
10062	31	31	31	31	31
10071	0	7	2	0	0
10165	31	31	31	31	31
10185	0	0	0	0	0

Table 5 continued

Seroconversion panel	First positive blood sample (day)				
	Elecsys	ADVIA centaur	Vitros Eci	Architect	AxSym
Total number of days	882	878	838	860	693
Number of panels tested	46	46	45	46	37
Mean number of days	19.2	19.1	18.6	18.7	18.7

All samples were compared with HCV-RNA PCR (first positive blood sample on day 0 for all seroconversion panels. Panels 10057 and 10071 were not tested by PCR)

n.t not tested. Seroconversion panels PHV901–PHV921 were manufactured by Seracare. Seroconversion panels 6212–10185 were manufactured by Zeptometrix

Table 6 Comparative statistical analysis (Wilcoxon test) of seroconversion sensitivity

	Statistical test result	Probability > (z)
ADVIA Centaur Anti-HCV vs. Elecsys Anti-HCV	−2	0.8516
Vitros Eci aHCV vs. Elecsys Anti-HCV	−4.5	0.6758
Vitros Eci aHCV vs. ADVIA Centaur Anti-HCV	0.5	0.9375
Architect Anti-HCV vs. Elecsys Anti-HCV	−1.0	0.3379
Architect Anti-HCV vs. Vitros Eci aHCV	−1.5	0.8125
AxSYM HCV vs. Elecsys Anti-HCV	−1.5	0.9258
AxSYM HCV vs. ADVIA Centaur Anti-HCV	2.5	0.8242
AxSYM HCV vs. Vitros Eci aHCV	4.5	0.7266
AxSYM HCV vs. Architect Anti-HCV	10	0.1953

blood donor and unselected routine serum samples, the specificity of the Elecsys Anti-HCV assay in our study was 99.5 and 99.4%, respectively. This was equivalent to the rates obtained with the Architect Anti-HCV, the ADVIA Centaur Anti-HCV, and the Vitros Eci aHCV assays. These findings are consistent with the results from other studies in which the specificity of the Elecsys Anti-HCV assay was compared with the Architect Anti-HCV, the ADVIA Centaur HCV, and Vitros Eci aHCV assays [11–14]. Previous studies have suggested that the Elecsys Anti-HCV assay is one of the most sensitive assays for the early detection of HCV in seroconversion samples [15]. Certainly, no significant difference was found in seroconversion sensitivity between the Elecsys Anti-HCV assay and the other state-of-the-art assays used as comparators in this study. In fact, seroconversion testing showed a difference of less than one day (3.2%) between assays in the detection of first positive blood sample. Unsurprisingly, differences between PCR-based tests and the anti-HCV antibody assays (approximately 19 days) were statistically significant, reflecting the greater sensitivity of molecular-based diagnostic methods.

In some cases, HCV testing does not lead to an unequivocal diagnosis of confirmed anti-HCV-positive or anti-HCV-negative status. Although confirmatory assays (such as HCV immunoblotting or HCV-RNA PCR) can be used, they may also result in indeterminate results. In studies based on a single blood sample (such as the current study), this may lead to difficulties in analysis. Where a follow-up or a retrospective analysis could have provided additional information, this was not possible in this study due to the limited study period. As a consequence, a limited number of inconclusives or indeterminates were found at each study center. However, as these were not included in the specificity calculations, this does not result in the inclusion of potentially false-positive samples.

HCV is a common, parenterally transmitted viral infection that is often asymptomatic and, therefore, difficult to diagnose clinically. Early diagnosis is, however, important to prevent progression to chronic HCV and its adverse clinical sequelae. Serologic tests for the detection of anti-HCV antibody, while less sensitive than RT–PCR, nonetheless provide a valuable first-line screening option for HCV infection as they are easy to perform and less expensive. As the present study has demonstrated, the Elecsys Anti-HCV assay provides excellent sensitivity and specificity for anti-HCV antibody detection in blood donor samples and routine clinical specimens. Its performance is similar to the other well-accepted, CE-marked Anti-HCV antibody assays that are in routine use.

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Conflict of interest None.

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