Original Article

Comparison of Roche Elecsys and Sysmex HISCL immunoassays for the screening of common blood-borne pathogens

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Background: We conducted a comprehensive comparison in the sensitivity, specificity, dilution sensitivity, and precision between two immunoassay systems, Roche Elecsys Cobas e 601 and Sysmex HISCL 5000, for the detection of hepatitis B virus surface antigen (HBsAg), antibody to hepatitis C virus (anti-HCV), treponemal antibodies (anti-TP), and human immunodeficiency virus (HIV).

Methods: One thousand unselected samples and 100 reserved weak reactive samples were tested by the two systems. Sensitivity and specificity were then calculated for each system. Seroconversion panels were used to assess the sensitivity in early stage detection. Dilution sensitivity was evaluated by dilution tests of several seroconversion panel samples. Evaluation of within-run and intermediate precision was conducted following EP-15A protocol.

Results: The consistency rates of the two systems for the detection of four pathogens were all over 99% among unselected samples. Both Elecsys and HISCL were observed to have high sensitivity and specificity in unselected samples and weak reactive samples. Seroconversion panel tests showed that Elecsys could identify positive results earlier than HISCL in HBsAg (1 out of 4), anti-TP (1 out of 2) and HIV (1 out of 12) panels. The results of the anti-HCV panels were comparable. In dilution tests, Elecsys could detect lower concentrations than HISCL in two anti-HCV samples and one anti-TP sample. The two systems had similar performance in dilution tests of HBsAg and HIV samples. Both Elecsys and HISCL had qualified intra-assay and inter-assay precision.

Conclusions: Both Elecsys and HISCL have good performance in the screening of four common bloodborne pathogens. The two systems are comparable and considered adequate for clinical use.

Keywords: Blood-borne pathogens; serological test; diagnostic performance; Roche Elecsys; Sysmex HISCL

Submitted Jan 29, 2019. Accepted for publication May 17, 2019.
doi: 10.21037/atm.2019.05.83
View this article at: http://dx.doi.org/10.21037/atm.2019.05.83

Introduction

Blood-borne infection is a major concern in transfusion procedures and for health care workers with occupational exposure to patients' blood (1,2). In recent decades, the human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and syphilis have been the main threats of transfusion-transmitted infections worldwide (3).

In China, blood screening for these pathogens is mandatory for blood donors and essential for most patients under hospitalization. This policy started in the 1990s and effectively decreased the incidence of transfusion-transmitted infection in the next decade (4,5). However, a recent study has reported that the overall positive rates of transfusion-transmitted infection were still 2.11% among

154,038 blood donors in southwestern China (6). This may be due to the window period between onset of infection and completion of seroconversion when serum concentrations of specific antigens or antibodies are insufficient for detection assays to identify a positive result (6,7). Therefore, detection assays of high sensitivity and strong ability in early stage detection are crucial to avoid false-negative results during blood screening.

Currently, enzyme-linked immunosorbent assay (ELISA), electrochemiluminescence immunoassay (ECLIA) and chemiluminescence immunoassay (CLIA) are the most widely used assays in the screening of blood-borne pathogens in China (8). ELISA is a proven method characterized by rapid detection, high sensitivity, and low costs. However, it also has several limitations including inherent instability, lack of automation, and the "Hook effect" (9). ECLIA and CLIA are emerging detection technologies with characteristics of superior diagnostic performance, high precision, good repeatability, and full automation. Xu *et al.* (10) evaluated the performance of ECLIA and ELISA on HBV detection in 359 serum samples. The results showed that ECLIA had better sensitivity than ELISA in weak reactive samples. Research by Wang *et al.* (11) indicated that ECLIA could detect positive results earlier than ELISA during seroconversion of HIV infection. Similar results were identified for comparison between CLIA and ELISA (12,13).

Despite these studies, little research has been done to compare ECLIA and CLIA in detecting these blood-borne pathogens, especially for the performance of early-stage detection. The present study aims to compare the comprehensive diagnostic performance of immunoassays from two commercially available detection systems, Roche Elecsys Cobas e 601 (Roche Diagnostics, Penzberg, Germany) (ECLIA) and Sysmex HISCL 5000 (Sysmex Corporation, Kobe, Japan) (CLIA), in the detection of HBV surface antigen (HBsAg), antibody to HCV (anti-HCV), antibody to treponemal antibodies (anti-TP), and HIV (anti-HIV 1/2 and HIV-1 p24Ag).

Methods

Clinical samples

One thousand unselected samples and 100 reserved weak reactive samples were collected from residual blood samples of hospitalized patients in Renmin Hospital of Wuhan University on the condition that they met the following criterion: (I) sample volume >1,000 μL; (II) a sample matrix of serum, heparin plasma, or EDTA plasma; (III) age of subject ≥18. Weak reactive samples were identified with Roche Elecsys system and were defined by the cut off index (COI) for each pathogen marker: COI ranges of 0.8< COI <4.0, 0.9< COI <5.0, and 0.5< COI <5.0 were respectively used for the detection of HBsAg, anti-HCV, and anti-TP. The study protocol was in accordance with the Helsinki Declaration and was approved by the Ethical Committee of Renmin Hospital of Wuhan University.

Seroconversion panels

A total of 29 seroconversion panels (SeraCare Life Sciences) were used to evaluate the sensitivity of the two systems in early stage detection (*Table S1*). Five panels were used for HBsAg detection, 10 for anti-HCV, 2 for anti-TP, and 12 for HIV (anti-HIV-1 and HIV-1 antigen p24).

Methodologies

Evaluation of sensitivity and specificity

Each clinical sample was separately tested by the two systems for the detection of four pathogen markers. All clinical samples were masked with a unique blind serial number. For inconsistent results, anti-HCV, HIV, and anti-TP samples were confirmed by Mikrogen Immunoblot Tests or recombinant immunobinding assay (RIBA) method; HBsAg samples were tested by a confirmatory test of each system at first, and then Abbott Architect HBsAg assay (Abbott Laboratories, Abbott Park, IL, USA) was used for final confirmation if necessary (*Figure 1*). All tests for a single clinical sample were completed within 24 hours. The concordance rate, sensitivity, and specificity of each system were then calculated.

Each seroconversion panel was simultaneously tested by Elecsys and HISCL, and the number of days needed to identify a positive result was recorded.

Evaluation of dilution sensitivity

Simulations of gradient concentration sample were completed by diluting seroconversion panels with negative serum into a series of titers (1:5, 1:20, 1:40, 1:80, …, up to 1:163,840). These simulations were sequentially tested by the two systems until the result turned negative.

Evaluation of precision

Within-run and intermediate precision were assessed according to the CLSI EP15-A guideline (14). Concentrations

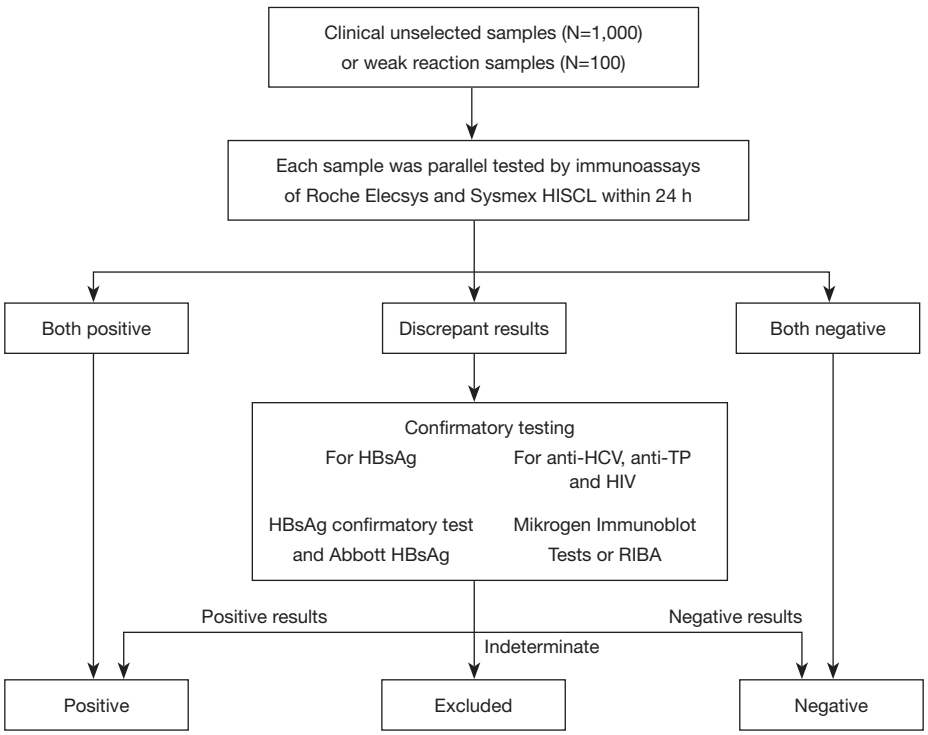

Figure 1 Algorithm used to test clinical samples.

of high level, medium level, and low-level samples for each pathogen marker were tested by Elecsys and HISCL 3 times a day and repeated for 5 days. Low and medium levels were defined according to precision control standards of Roche Elecsys system. High-level samples were selected from serum samples with high COI value (>100). Coefficients of variation (CV%) were calculated.

Detection systems and immunoassays

Roche Elecsys Cobas e 601 (Roche Diagnostics) and Sysmex HISCL 5000 (Sysmex Corporation) are both fully-automated immunoassay analyzers capable for simultaneous detection of antigens and antibodies in serum or plasma, but their mechanisms in detecting antigen-antibody complex are different. For the Cobas e 601, the immune complex attached to the microparticles is magnetically sequestered on the electrode, and the chemiluminescence is electrically induced and measured. Meanwhile, for the HISCL 5000, demagnetization separation technology is used to separate the immune complex and free impurities and chemiluminescence is then measured by filter switching technology.

The immunoassays used for each pathogen are listed in *Table 1*. Most of them were qualitative assays with the exception of HISCL HBsAg.

Results

The concordance rates of Elecsys and HISCL were higher than 99% for all pathogen markers in the 1,000 unselected clinical samples (*Table 2*). A sensitivity of 96.59% for HBsAg and 100% for both anti-HCV and anti-TP was obtained for Elecsys, while the corresponding values were 97.73%, 94.12%, and 100% for HISCL. No positive sample was identified for HIV detection. Both Elecsys and HISCL had an excellent specificity of higher than 99%. Similar results were observed for 100 weak reactive samples (*Table 3*).

Results of seroconversion panel tests are listed in *Table S1*. Elecsys could identify a positive result earlier than HISCL in three panels: one HBsAg panel (PHM940), one anti-TP panel (PSS901), and one HIV panel (PRB964). However, the results of the 10 anti-HCV panels were controversial: three panels (PHV919, PHV925, and PHV926) favored Elecsys, while three other panels (PHV913, PHV920, and PHV922) favored HISCL.

Table 1 List of immunoassays used for each pathogen marker

Marker/immunoassay	Solid phase	Conjugate phase
HBsAg		
Elecsys HBsAg II	Two biotinylated monoclonal anti-HBsAg antibodies (mouse)	Monoclonal anti-HBsAg antibody (mouse), polyclonal anti-HBsAg antibodies (sheep) labeled with ruthenium complex
HISCL HBsAg	Biotinylated monoclonal anti-HBsAg antibodies (mouse)	Monoclonal anti-HBsAg antibodies (mouse) labeled with ALP
Anti-HCV		
Elecsys anti-HCV II	Biotinylated HCV-specific antigens, HEPES	HCV-specific antigens labeled with ruthenium complex
HISCL anti-HCV	Biotinylated HCV-specific antigens	Monoclonal anti-human IgG antibodies (mouse) labeled with ALP
Anti-TP		
Elecsys Syphilis	TP-specific recombinant antigens (*E. coli*)-biotin	TP-specific recombinant antigens (*E. coli*)-Ru(bpy)
HISCL anti-TP	Biotinylated TP-specific recombinant antigens (Tp15, 17, 47 kDa)	TP-specific recombinant antigens labeled with ALP (Tp15, 17, 47 kDa)
HIV (anti-HIV-1/2 and HIV-1 p24Ag)		
Elecsys HIV combi PT	Biotinylated monoclonal anti-p24 antibodies (mouse), biotinylated HIV-1/2-specific recombinant antigens (*E. coli*), biotinylated HIV-1/2 specific peptides	Monoclonal anti-p24 antibodies (mouse), HIV-1/2 specific recombinant antigens, HIV-1/2 specific peptides labeled with ruthenium complex
HISCL HIV Ag + Ab	Biotinylated monoclonal anti-p24 antibodies, HIV antigens	HIV antigens/monoclonal anti-p24 antibodies labeled with ALP

In the dilution tests of certain seroconversion panel samples, Elecsys could detect titers up to 1:201 and 1:5,120 for two HBsAg panels (PHM937 and PHM939), 1:320 and 1:2,560 for two anti-HCV panels (PHV917 and PHV919), and 1:1,280 for one anti-TP panel (0820-0214-19). The corresponding results for HISCL were 1:40 and 1:20,480 for HBsAg panels, 1:5 and 1:20 for anti-HCV panels, and 1:160 for the anti-TP panel. The two systems could detect an equal dilution ratio (1:40) for the HIV panel PRB976.

Results of precision evaluation showed that both Elecsys and HISCL had a stable performance in all tests in spite of the concentration levels. Within-run and intermediate CV% ranged from 0% to 6.8%, with the results meeting the requirements of the manufacturer.

Discussion

The screening of blood-borne pathogens is crucial to avoid transfusion-transmissible infections and cross infections in hospital, yet the requirements for optimal detection methods are different in two scenarios (15). For screening in blood donations, sensitivity is the most important property to identify every single sample that is potentially infected. In addition, the capability of early-stage detection is also important since infections caused by these pathogens could be asymptomatic and hard to detect in the window period. However, for regular screening in hospitalized patients, minimizing false-positive results should be considered in order to save medical resources and patients' utility.

We conducted a comprehensive comparison between Roche Elecsys and Sysmex HISCL in their detection performance on blood-borne pathogens, with reference to ECLIA and CLIA respectively. Results of the unselected clinical samples and weak reactive samples indicated that both Elecsys and HISCL had excellent sensitivity and specificity, and the concordance rate of the two systems exceeded 95% in all tests. Additionally, they were fully-automatic analyzers with good within-run and intermediate precision. Thus, our results suggest that both Elecsys and HISCL are capable of screening blood-borne pathogens, regardless of the property concerned.

These results are consistent with previous studies. Tao

Table 2 Detection results of clinical unselected samples by Elecsys and HISCL

Test results	HBsAg		Anti-HCV		Anti-TP		HIV	
	Elecsys	HISCL	Elecsys	HISCL	Elecsys	HISCL	Elecsys	HISCL
N vilid samples*	999		997		1,000		1,000	
N indeterminate samples	6		7		2		2	
Concordance rate (%)	99.40		99.30		99.80		99.80	
FP (N)	0	0	2	1	2	0	1	1
FN (N)	3	2	0	1	0	0	0	0
TP (N)	85	86	17	16	14	16	0	0
TN (N)	911	911	978	979	984	984	999	999
Sensitivity (%)	96.59	97.73	100.00	94.12	100.00	100.00	–	–
Specificity (%)	100.00	100.00	99.80	99.90	99.80	100.00	99.90	99.90

*, indeterminate samples were excluded if no clear result was obtained in confirmatory tests. FP, false positive; FN, false negative; TP, true positive; TN, true negative.

Table 3 Detection results of weak reactive samples by Elecsys and HISCL

Test results	HBsAg		Anti-HCV		Anti-TP	
	Elecsys	HISCL	Elecsys	HISCL	Elecsys	HISCL
N vilid samples*	98		97		97	
N indeterminate samples	2		4		6	
Concordance rate (%)	98.00		96.00		94.00	
FP (N)	0	0	1	0	3	0
FN (N)	0	0	0	0	0	0
TP (N)	11	11	14	14	41	44
TN (N)	87	87	82	83	53	53
Sensitivity (%)	100.00	100.00	100.00	100.00	100.00	100.00
Specificity (%)	100.00	100.00	98.80	100.00	94.64	100.00

*, indeterminate samples were excluded if no clear result was obtained in confirmatory tests. FP, false positive; FN, false negative; TP, true positive; TN, true negative.

et al. (16) screened 13,767 serum samples from 13 centers in China and obtained a sensitivity of 100% and a specificity of 99.81% for Elecsys in detecting anti-TP. Similar data on sensitivity and specificity of HISCL was reported by An *et al.* (17). Elecsys anti-HCV II assay showed a sensitivity of 100% and a specificity of 99.66% in 7,726 routine samples from the Asia-Pacific region (18), while research by Feng *et al.* (19) revealed that HISCL anti-HCV assay had a sensitivity of 98.97% and specificity of 100% in 1,048 samples from China. Other studies also indicated that both Elecsys and HISCL had superior performance in the detection of HBsAg and HIV (20-22).

Results of seroconversion panel tests demonstrated that Elecsys had a slightly better performance than HISCL in early detection of all pathogen markers except for anti-HCV. Interestingly, Feng *et al.* (19) compared anti-HCV assays of these two systems and found that Elecsys had a superior seroconversion sensitivity to HISCL (detection rate: 64.62% for Elecsys and 46.15% for HISCL). This advantage may be explained by the difference between

ECLIA and CLIA in the detection mechanism. ECLIA yields a specific chemiluminescence reaction initiated by electrochemistry on the surface of the electrode, which is easier to control and more accurate than when initiated by simple mixing of the compound (CLIA) (23). Similar advantages were also observed in dilution tests showing that Elecsys could detect lower titers in several seroconversion panels of HBsAg, anti-HCV, and anti-TP. However, further studies involving samples from different populations are needed to confirm these findings.

Our study had some limitations. First, clinical samples used in our study were retrospectively collected from residual samples of hospitalized patients. Therefore, clinical diagnosis information was not available and could not be used to confirm positive results. Secondly, we did not collect or restrict the genotypes of these pathogens, and so further comparison based on subtypes was not possible. Lastly, no positive HIV samples were collected in our study.

Nevertheless, to the best of our knowledge, this was the first study to compare multiple immunoassays of Elecsys and HISCL in the screening of four common blood-borne pathogens. Our results suggested that both Elecsys and HISCL had superior performance in the detection of HBsAg, anti-HCV, anti-TP, and HIV. The two systems are both adequate for clinical use, but Elecsys probably may have some advantages in early stage detection due to the features of ECLIA.

Acknowledgments

This study was supported by Roche diagnosis (Shanghai) Limited. The funder was also responsible for the supplement of detection reagents and for the support of corresponding detection technology.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study protocol was in accordance with the Helsinki Declaration and was approved by the Ethical Committee of Renmin Hospital of Wuhan University.

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Cite this article as: Xu W, Tong Y, Li Y. Comparison of Roche Elecsys and Sysmex HISCL immunoassays for the screening of common blood-borne pathogens. Ann Transl Med 2019;7(14):300. doi: 10.21037/atm.2019.05.83

Supplementary

Table S1 Results of seroconversion panel tests

Marker	Panel No.	Genotype	Number of positive bleeds/total number of bleeds tested	
			Elecsys	HISCL
HBsAg	PHM937	A	3/5	3/5
	PHM939	A	3/5	2/5
	PHM940	A	1/8	0/8
	PHM941	A	7/9	6/9
	PHA207	–	18/20	18/20
Anti-HCV	PHV924	2b	3/6	2/6
	PHV922	3a	2/6	5/6
	PHV920	1a	7/9	8/9
	PHV926	3a	5/5	0/5
	PHV925	1a	3/5	1/5
	PHV928	1a	0/9	0/9
	PHV927	1a	0/5	0/5
	PHV917	2b	6/9	6/9
	PHV913	2b	2/4	3/4
	PHV919	–	7/7	3/7
Anti-TP	PSS901	–	4/9	3/9
	0820-0214	–	18/20	18/20
HIV	PRB973	–	2/4	2/4
	PRB967	–	3/6	3/6
	PRB975	–	1/5	1/5
	PRB963	–	2/7	2/7
	PRB977	–	2/4	2/4
	PRB962	–	2/6	2/6
	PRB969	–	3/10	3/10
	PRB964	–	1/6	0/6
	PRB968	–	4/10	4/10
	PRB970	–	4/4	4/4
	PRB974	–	2/4	2/4
	PRB976	–	2/4	2/4