EDITORIAL
DOI: 10.3904/kjim.2009.24.4.299

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Anti-HCV Signal-to-Cutoff Ratio in Predicting Hepatitis C Viremia

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Hepatitis C virus (HCV) is one of the major etiologic agents of chronic liver diseases. Early and effective screening test of HCV was developed since the virus was first identified in 1989. The screening test of HCV is anti-HCV antibody test by immunoassays and the infection status is confirmed by recombinant immunoblot assay (RIBA) and nucleic acid testing of HCV.

Anti-HCV test was firstly developed by enzyme-linked immunosorbent assay which has relatively good sensitivity and specificity. Recently, it has been replaced by automated chemiluminescent immunoassay (CLIA) because of laboratory automation trend and advantages of its improved sensitivity and specificity. But, sometimes the screening immunoassays have been too much improved their sensitivities. Especially among populations with low (<10%) prevalence of HCV infection, assays for anti-HCV antibodies show high false-positive rates [1]. This is particularly problematic in asymptomatic persons with no clinical information available or in those who are being tested for the first time and in determining the need for postexposure follow-up. Therefore, positive results for HCV antibody screening tests require confirmation with other more specific supplementary tests such as RIBA or a nucleic acid test [2].

However, some laboratories lack an established laboratory standard for such supplemental testing or lack understanding of performance and interpretation of the screening and supplemental HCV tests. The high cost of the supplemental tests also makes them unavailable in many laboratories. One of the simple methods is sample Signal-to-Cutoff (S/CO) ratio of anti-HCV immunoassay. So the Center for Disease Control and Prevention (CDC) published guidelines that recommended supplemental tests to be based on anti-HCV assay S/CO ratios [2]. Generally, the S/CO value of more than 1 is regarded as positive in CLIA test. However, owing to improvement in the sensitivity of HCV tests, it is suggested that more accurate standard for reflecting positive HCV infection is needed. Thus, establishing optimal S/CO ratio is prerequisite for avoiding unnecessary further HCV tests which are currently adopted for increasing the reliability of diagnosis. In this regard, S/CO ratio is thought to better reflect HCV infection status of patients.

However, significant value of S/CO ratio determining true infection status seems to be different from company to company. Thus, the difference in the ratio from reagents should be taken into account when judging HCV viremia.

According to the CDC guideline, reflex supplemental testing may be limited to screening test-positive patients with average S/CO ratios <3.8, as anti-HCV positive samples with average S/CO ratios ≥3.8 would be highly predictive of the RIBA positivity (≥95%) [2]. Other studies have also evaluated the clinical significance of low S/CO ratios and found good correlation between S/CO ratio of anti-HCV and HCV viremia [3-8]. Some studies even suggested the elimination of reflex supplemental testing in samples with low S/CO ratio in order to save costs and reduce unnecessary testing [5,8]. These time and cost saving efforts have been reflected in another way in the study by Seo et al. They evaluated the utility of low S/CO ratio in predicting HCV viremia and in deciding whether to opt for qualitative or quantitative HCV RNA test in a HCV antibody positive patient. The authors suggest the use of qualitative HCV RNA testing in patients with anti-HCV S/CO ratio <10.9 and quantitative HCV RNA testing in patients with anti-HCV ≥10.9. This is a novel approach to reduce time and cost of diagnosis, but unfortunately,

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may not yet be universally applicable.

The authors of this article Seo et al. have based their cutoff point for the S/CO ratio on results from Abbott second-generation anti-HCV enzyme immunoassay, so cutoff points with other enzyme immunoassays or chemiluminescence immunoassays should be further evaluated for application in other laboratory settings. In addition, anti-HCV titer may decrease with spontaneous HCV resolution or clearance after therapy [9]. In this case, low anti-HCV S/CO ratio may not automatically require a qualitative RNA testing and clinicians must be aware of such influence on serologic testing. As mentioned in the discussion, the study may be subjected to selection bias due to the inclusion and exclusion criteria and may not be quite applicable in patients with chronic hepatitis or HCV resolution with or without therapy. Furthermore, the authors have discussed that the lower detection limit of the HCV qualitative test may possibly have misclassified the patients and influenced the results. With development of transcription mediated amplification assays, the sensitivity of qualitative assays has been improved to have a lower detectable limit of 5 IU/mL [10]. This may be another factor influencing the clinical application of the S/CO ratio.

Although the CDC and others have examined the correlation of S/CO ratio and RIBA results, the high cost and indeterminate results not infrequently seen in the gray zone of anti-HCV titer may render the RIBA assay obsolete as supplemental verification test [11]. The Vitros Anti-HCV assay has been approved by the Food and Drug Administration and an S/CO ratio of 8.0 was set as the screening test positive value to determine the need for reflex supplemental tests. But, a study performed in my laboratory, the cutoff of S/CO ratios were as follows: Elecsys assay, ≥200 (95.7%); Architect assay, ≥3 (94.9%); Vitros assay, ≥7.0 (95.7%); Access assay, ≥3 (94.7%) [6]. Details of the four automated CLIA reagents were the Elecsys Anti-HCV assay on the Cobas e 411 analyzer (Roche Diagnostics, Mannheim, Germany), the Architect Anti-HCV assay on the Architect i2000 system (Abbott Laboratories, Abbott Park, IL, USA), the Vitros Anti-HCV assay on the Vitros ECiQ Immunodiagnostic System (Ortho-Clinical Diagnostics, Raritan, NJ, USA), and the Access HCV Ab PLUS assay (Bio-Rad Laboratories, Redmond, WA, USA) on the UniCel DxI 800 analyzer (Beckman-Coulter, Fullerton, CA, USA).

Nucleic acid tests with improved sensitivity may supplant former diagnostic tools, but remain expensive and unavailable in many clinical settings. A guidance for the optimal diagnostic approach is necessary and may be found in the S/CO ratio of HCV antibody screening test, but further evaluation is needed for broader clinical application. Because many commercial reagents are on the market and accurate correlation studies with clinical conditions are needed.

The paper of Seo et al. showed that S/CO ratio is valuable in determining HCV viremia. Furthermore, they proposed the critical level of S/CO which may help discriminate the occasions when HCV RNA quantitative or qualitative test are needed. These results may be applicable effectively to detect HCV viremia for users of the same test method. Although their results are promising in terms of setting-up new index for HCV viremia, further studies are needed to each laboratory to develop their own index for their diagnostic methods. In addition, optimization of follow-up setting for their studies is expected. **(Korean J Intern Med 2009;24: 299-301)**

REFERENCES

1. Sugitani M, Inchauspe G, Shindo M, Prince AM. Sensitivity of serological assays to identify blood donors with hepatitis C viremia. Lancet 1992;340:249-250.
2. Alter MJ, Kuhnert WL, Finelli L; Centers for Disease Control and Prevention. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. Centers for Disease Control and Prevention. MMWR Recomm Rep. 2003;7;52(RR-3):1-13.
3. Ren FR, Lv QS, Zhuang H, et al. Significance of the signal-to-cutoff ratios of anti-hepatitis C virus enzyme immunoassays in screening of Chinese blood donors. Transfusion 2005;45:1816-1822.
4. Bossi V, Galli C. Quantitative signal of anti-HCV by an automated assay predicts viremia in a population at high prevalence of hepatitis C virus infection. J Clin Virol 2004;30:45-49.
5. Contreras AM, Tornero-Romo CM, Toribio JG, et al. Very low hepatitis C antibody levels predict false-positive results and avoid supplemental testing. Transfusion 2008;48:2540-2548.
6. Kim S, Kim JH, Yoon S, et al. Clinical performance evaluation of four automated chemiluminescence immunoassays for hepatitis C virus antibody detection. J Clin Microbiol 2008;46:3919-3923.
7. Kim YK, Kim BH, Jin ES, et al. Positive predictability and predictive factors of the third generation anti-hepatitis C virus (HCV) ELISA test for HCV infection. Korean J Gastroenterol 2005;45:181-188.
8. Oethinger M, Mayo DR, Falcone J, Barua PK, Griffith BP. Efficiency of the ortho VITROS assay for detection of hepatitis C

virus-specific antibodies increased by elimination of supplemental testing of samples with very low sample-to-cutoff ratios. J Clin Microbiol 2005;43:2477-2480.

9. Kondili LA, Chionne P, Costantino A, et al. Infection rate and spontaneous seroreversion of anti-hepatitis C virus during the natural course of hepatitis C virus infection in the general population. Gut 2002;50:693-696.
10. Chevaliez S, Pawlotsky JM. How to use virological tools for optimal management of chronic hepatitis C. Liver Int 2009;29 Suppl 1:9-14.
11. Kiely P, Wilson D. Results of HCV screening of volunteer blood donors with a chemiluminescent immunoassay and a second- or third-generation EIA: overlap of false-positive reactivity and its impact on donor management. Transfusion 2000;40:580-584.