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# The importance and role of anti-HCV signal/cutoff ratio in diagnosis of hepatitis C virus infection

## Anti-HCV sinyal/eşik değer oranının Hepatit C virüs enfeksiyonu tanısında rolü ve önemi

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**Summary**

**Aim:** Different signal/cutoff values for different commercial kits are used to determine the samples that would predict a true antibody response for Hepatitis C Virus infection. The aim of this study is to determine a specific signal/cutoff ratio with the commercial kit that is used routinely in our laboratory that would predict a true antibody positive result 95% of the time regardless of the anti-HCV prevalance.

**Material and Methods:** A total number of 309 anti-HCV positive samples that were tested with the architect anti-HCV assay (Abbott Laboratories, IL, USA) were reviewed retrospectively and categorized according to their signal/cutoff ratio. These samples were retested with LIA (Innogenetics N.V., Belgium). ROC-curve analysis in SPSS 17.0 statistical package programme was used for data analysis.

**Results:** The signal/cutoff ratio 3.27 is determined as the cutoff point that predicts a true antibody positive result in 94.9% (positive predictive value 94.9 %, specificity 81.4%, sensitivity 91.2%) of the cases according to the ROC curve analysis.

**Conclusion:** A stepwise approach is appropriate for evaluation of patients positive for anti-HCV. It is important for laboratories to determine a cutoff point to distinguish between a low and high positive Anti-HCV result. With the architect anti-HCV assay (Abbott, USA), in cases with signal/cutoff >3.27, the line immunoassay will be positive in most patients, so supplementary testing in such individuals is not needed.

**Key Words**: Anti-HCV, hepatitis C, signal/cutoff ratio, diagnosis.

***Özet***

***Amaç:*** *Hepatit C virüs enfeksiyonunda farklı ticari kitler ile gerçek antikor pozitifliğini öngören farklı Anti-HCV sinyal/eşik değer oranları belirlenmiştir. Bu çalışmanın amacı, laboratuvarımızda rutin olarak kullanılan ticari kit için anti-HCV prevalansından bağımsız olarak %95 gerçek antikor olumluluğunu öngören spesifik bir sinyal/eşik değer oranı belirlemektir.*

***Gereç ve Yöntem:*** *Architect anti-HCV (Abbott Laboratories, IL, ABD) kiti ile daha önce test edilen 309 anti-HCV pozitif örnek sinyal/eşik değerlerine göre sınıflandırıldı. Bu örnekler LIA (Innogenetics N.V., Belçika) ile tekrar test edildi. Veri analizi için 17.0 SPSS paket programındaki ROC eğri analizi kullanıldı.*

***Bulgular:*** *ROC eğrisi analizine göre 3.27 sinyal/eşik değer oranı, gerçek antikor pozitifliğini öngören eşik değer olarak bulundu (pozitif prediktif değer %94.9, özgüllük %81.4, duyarlılık %91.2).*

***Sonuç:*** *Anti-HCV pozitif bulunan hastaların değerlendirilmesinde basamaklı bir yaklaşım uygundur. Laboratuvarların, düşük ve yüksek anti-HCV pozitifliğini ayırt edebilecek bir eşik değer belirlemesi önemlidir. Architect anti-HCV testi (Abbott, ABD) ile sinyal/eşik değeri >3.27 olan örneklerde line immunoassay testi hastaların çoğunda pozitif olarak bulunacağından, bu hastalarda bu tip bir destekleme testinin uygulanmasına gerek yoktur.*

***Anahtar Sözcükler:*** *Anti-HCV, hepatit C, sinyal /eşik oranı, tanı.*

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## Introduction

There are a variety of diagnostic tests available for Hepatitis C Virus (HCV) infection and substantial differences exist in testing practices between laboratories. An ideal testing strategy for HCV would correctly identify whether an individual has ever been infected (serostatus) as well as whether that individual is currently infected (viral status) (1). Testing for HCV infection begins with detection of antibodies to recombinant or synthetic HCV proteins using enzyme immunoassays (EIA). Because of the false positive results especially in low prevalence settings, positive anti-HCV EIA results are usually confirmed by recombinant immunoblot tests and strip immunoblot assays (RIBA). The current clinical practice after identifying a positive anti-HCV result is to measure HCV RNA to assess whether viremia is present (2). On the other hand, several studies have suggested that RIBA has no place in the evaluation of anti-HCV EIA results in the clinical setting (3-6).

Anti HCV EIA results are interpreted by comparing the absorbance reading of the patient with a defined cutoff value. More recently, some investigators have advocated dividing EIA signal-to-cutoff ratio (s/co) into three levels as high positive, low positive and negative. High positive samples would be clearly designated positive with few false positives. Samples found to be low positive would require a supplementary test as RIBA (7,8).

A variety of HCV testing strategies have been recommended by different authorities (8, 9, 10). In 2003, to facilitate practice of reflex supplemental testing, the Centers for Disease Control (CDC) extended HCV testing algorithm to include an option that uses the s/co ratios of EIA results to minimize the number of specimens that require supplemental testing. According to these recommendations, laboratories should use only screening tests that have been evaluated for this purpose and for which high s/co ratios have been demonstrated to predict a supplemental-test–positive ≥95% of the time among all populations tested. Screening-test–positive samples with high s/co ratios can be reported as anti-HCV positive without supplemental testing. For the EIA positive samples with low s/co values, supplemental testing preferably RIBA should be performed (8).

Different s/co values for different commercial kits are used to determine the samples that would predict a true antibody response. The aim of this study is to determine a specific s/co ratio with the commercial kit that is used routinely in our laboratory that would predict a true antibody positive result 95% of the time regardless of the anti HCV prevalence.

## Materials and Methods

A total number of 309 anti-HCV EIA positive samples that have been submitted to Ege University Hospital, Department of Medical Microbiology Virology Laboratory between January 2007-July 2009 for anti-HCV and HCV RNA testing were included to the study. These samples were previously tested with the Architect Anti-HCV assay (Abbott Laboratories, IL, USA) run on the i2000SR analyser and tested for HCV RNA with either the COBAS Ampliprep/COBAS Taqman HCV test (Roche Molecular Systems Inc Branchburg, NJ,USA) or the COBAS Amplicor Hepatitis C Virus test v2.0(Roche Molecular Systems Inc Branchburg, NJ,USA). Anti-HCV positive samples were reviewed retrospectively, and categorized according to their s/co ratio. Their RNA results were noted and samples were retested with Line immunoassay (Innogenetics Ghent, Belgium) from the plasma samples stored at -80°C. To establish a specific level of s/co ratio that predicts a positive LIA in 95% of the cases, samples tested by EIA were stratified into16 groups as 1-2, 2.1-3, 3.1-4, 4.1-5, 5.1-6, 6.1-7, 7.1-8, 8.1-9, 9.1-10, 10.1-11, 11.1-12, 12.1-13, 13.1-14, 14.1-15, 15.1-16, >16 and in order to use ROC curve analysis, each group consisted of approximately 10-30 sample size that were randomly selected.

The screening assay the Architect Anti-HCV uses putative structural and nonstructural proteins of the HCV genome. It contains recombinant antigens representing the core, NS3 and NS4 proteins (HCr43, c100-3). HCr43 is composed of two non-contiguous coding regions of the HCV genome sequence, 33c and the core. C100-3 is a recombinant protein contained within the putative nonstructural region (NS3 and NS4). The assay is a two step immunoassay using chemiluminescent microparticle immunoassay technology (CMIA).

The analysis of HCV RNA was previously performed by either the COBAS Ampliprep/COBAS Taqman HCV test or the COBAS Amplicor Hepatitis C Virus test v2.0. COBAS Ampliprep/COBAS Taqman HCV test is an invitro nucleic acid amplification test for the quantitation of HCV RNA. Specimen preparation is automated using the COBAS Ampliprep instrument with amplification and detection automated using the COBAS Taqman Analyzer. The test uses reverse transcription and PCR amplification primers that define a sequence within the highly conserved region of the 5' untranslated region of the HCV genome. The lower detection limit of the COBAS TaqMan HCV assay is 15 IU/ml. The COBAS Amplicor Hepatitis C Virus test v2.0 is a qualitative

diagnostic test for the detection of HCV on the COBAS Amplicor Analyzer. The limit of detection is 50 IU/ml.

The InnoLIA HCV Score is a third generation line immunoassay (LIA) which incorporates HCV antigens derived from the core region, the E2 hypervarible region, the NS3 helicase region, the NS4A, NS4B, and NS5A regions. In addition to the six antigen lines, four control lines are coated on the strips. Results are expressed as ±, 1+, 2+, 3+,4+ according to the intensity of the bands compared to the controls. For the purpose of this evaluation, samples were scored as positive if a reactivity of ± or more towards antigens encoded from at least two different HCV regions were detected, while other reactivity patterns were classified as indeterminate. All the commercial tests were performed and interpreted following the manufacturers' guidelines.

The SPSS 17.0 statistical package programme was used for data analysis (SPSS Inc, Chicago, IL, USA). ROC-curve analysis was used to determine the threshold value and crosstabulations were made to estimate the positive predictive value, spesificity and sensitivity. HCV RNA results in relation to s/co ratios were analyzed with the chi-square test. Ethical approval was provided by Ege University Research Ethics Committee.

**Results**

Overall, of the 309 samples reactive for anti-HCV by the Architect Anti-HCV assay, a total number of 226 samples were positive, 24 were indeterminate and 59 were negative by LIA. The distribution of Architect reactivity ratios expressed as s/co in relation to LIA results are shown in (Table-1).

The s/co ratio 3.27 is determined as the cutoff point that predicts a true antibody positive result in 94.9% (positive predictive value 94.9 %, specificity 81.4%, sensitivity 91.2%) of the cases according to the ROC curve analysis. For the ROC curve analysis indeterminate LIA results are excluded. LIA results in relation to the determined cutoff point are shown in (Table-2).

The Architect s/co values were directly correlated with the presence of HCV-RNA: a PCR positivity was found in 2.2% of the samples with S/CO ratios 1-2 and, in 88.9% of samples with a s/co >16 (chi square for linear trend; $P < 0.001$). When the s/co 3.27 was taken as the threshold value, only 2.4% of the samples below the determined cutoff value were PCR positive, and the positivity rate increased to 60.2% among samples with s/co >3.27 ($P< 0.001$). The relation between the Architect s/co ratios and HCV RNA are shown in (Figure-1).

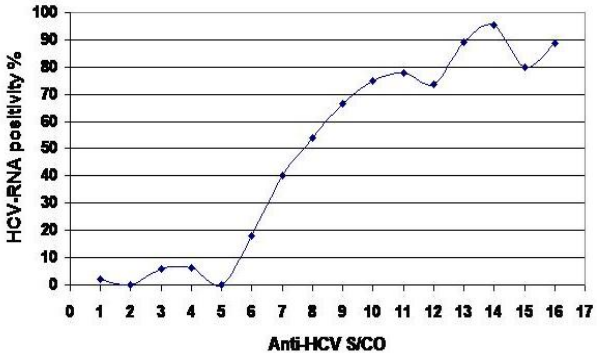


**Figure-1.** The relation between architect s/co ratios and HCV RNA.

Overall, 138 (61.6%) out of 224 samples with LIA positive results were HCV RNA positive while HCV RNA was not evidenced in samples with indeterminate and negative LIA results. The distribution of reactivity scores in relation to both HCV RNA and LIA are summarized in (Table-3).

**Table-1.** HCV LIA results at different anti-HCV EIA reactivity s/co levels.

| Anti-HCV s/co | Positive (%) | Indeterminate (%) | Negative (%) |
|---|---|---|---|
| 1.00-2.00 | 6 (13.3%) | 9 (20%) | 30 (66.7%) |
| 2.10-3.00 | 9 (29%) | 6 (19.4%) | 16 (51.6%) |
| 3.10-4.00 | 12 (70.6%) | 2 (11.8%) | 3 (17.6%) |
| 4.10-5.00 | 11(68.8%) | 2 (12.5%) | 3 (18.8%) |
| 5.10-6.00 | 9(56.3%) | 3 (18.8%) | 4 (25.0%) |
| 6.10-7.00 | 9 (81.8%) | 1 (9.1%) | 1 (9.1%) |
| 7.01-8.00 | 9 (90%) | 0 | 1(10.0%) |
| 8.10-9.00 | 11 (84.6%) | 1 (7.7%) | 1 (7.7%) |
| >9.1 | 150 (100%) | 0 | 0 |

**Table-2.** LIA results in relation to the determined threshold point.

| | | | Anti-HCV s/co | | Total |
|---|---|---|---|---|---|
| | | | +(≥3,27) | -(<3,27) | |
| **LIA Result** | + | Number of samples (%) | 206 (91.2%) | 20 (8.8%) | 226 |
| | - | Number of samples | 11 (18.6%) | 48 (81.4%) | 59 |
| **Total** | | Number of samples | 217 (76.1 %) | 68 (23.9%) | 285 |

**Table-3.** Distribution of samples below and above the determined value by architect anti-HCV, and relationship with the LIA and PCR results.

| AntiHCV s/co | LIA neg RNA neg | LIA neg PCR pos | LIA indet PCR neg | LIA indet PCR pos | LIA Pos PCR neg | LIA pos PCR pos | Total |
|---|---|---|---|---|---|---|---|
| <3.27 | 49 | 0 | 15 | 0 | 17 | 2 | 83 |
| >=3.27 | 11 | 0 | 9 | 0 | 70 | 136 | 226 |

Neg: negative, pos: positive, indet: indeterminate

## Discussion

Chronic hepatitis C is a global health problem, and according to recent World Health Organization data the overall prevalence of hepatitis C virus (HCV) infection is estimated to be 2%, with over 123 million people infected worldwide (11). Since there are considerable medical and social implications for people designated as having the HCV infection, it is important to properly classify the HCV infection status of a patient. Careful use of the available assays is essential for accurate and efficient diagnosis of the HCV infection. The recommended anti-HCV testing algorithm of CDC has been expanded to include an option that uses s/co ratios of screening-test-positive results. The aim of this option is minimizing the number of specimens that require supplementary testing and providing a result that has a high probability of reflecting the person's true antibody status (8).

In a study that used decision analysis to evaluate different HCV testing strategies, assessing the outcomes, including the cost, sensitivity and specificity of each strategy with regard to detecting serostatus and viral status, RIBA testing on the bases of low EIA s/co and then PCR for all positive and indeterminate samples, was found to be the best strategy when the prevalence of HCV in the group tested was below 20% (1).

The s/co ratios on which RIBA testing should be performed vary according to the kit manufacturer and to the population tested, so it must be established for each laboratory. Reports from the CDC show that the average s/co ratio >3.8 is highly predictive of the true anti-HCV status for kits manufactured by Ortho-Clinical Diagnostics (Ortho HCV version 3.0 ELISA, Raritan, NJ, USA) and by Abbott EIA (Abbott EIA 2.0, Chicago, IL, USA) and ratios >8.0 for kits manufactured by VITROS anti-HCV (8,12,13). Reflex supplemental testing could be limited to screening test-positive samples with ratios below the determined threshold ratio. Even though there are sensitivity studies on modified version of the Architect Anti-HCV assay, few published studies have documented experience on the determination of the s/co threshold value of the assay to compare our results (14,15). As far as the reviewed literature indicates, this is the first report on the determination of a threshold ratio for the Architect Anti-HCV assay by comparing the s/co values to both LIA and HCV RNA test results. In a study conducted with Architect Anti-HCV EIA, the authors obtained s/co ratio $\geq$3.0 as the threshold ratio that had a high concordance with both the HCV RNA positive test and the clinical findings (16). In another study, HCV s/co values are compared with HCV RNA and a critical level for false-positivity was found to be s/co value 5 for the Architect anti-HCV assay (17). In the current study, the comparison between the Architect s/co value and LIA test results indicate that a strong reactivity by the screening assay predicts the positivity by the LIA. The s/co ratio 3.27 is determined as the threshold point that predicts a true antibody positive result in 94.9% of the cases according to the ROC curve analysis. Beyond that threshold, the LIA does not add specificity to the screening test.

The benefit of determining serostatus of the patient in the clinical setting has come under question (9,18). People incorrectly labeled as anti-HCV positive are subjected to additional physician visits and repeated HCV RNA measurements. Family members may also be subjected to additional testing unnecessarily, so even in the clinical setting it is important to determine the true status of the patient in relation to HCV infection (8). In this study, out of 68 patients with s/co levels $\leq$ 3.27, 48 patients (%70.6) were negative by LIA. Without the performance of the LIA, these patients and their family members would have been subjected to additional follow-up tests. On the other hand, even though in this study HCV RNA positivity was not recorded in any of the patients with low s/co ratios and LIA negative results, there may have been a few individuals with this profile who were actually exposed to HCV and labeled as HCV negative. It is important to perform PCR in a patient with a high risk of acquiring HCV infection or a patient suspected of an acute HCV infection.

The main problem related to LIA testing concerns the indeterminate results. Some possible causes are the seroconversion phase during which EIA is already positive (12, 19, 20) or seroreversion in patients who

spontaneously eliminate HCV. In this group of individuals, antibodies against some antigenic fractions have already turned negative for LIA but they may be sufficient to cause an EIA positive result (19,21). Other factors that cause indeterminate results may be related to kit performance or to patient immunoresponse variability (22,23). Overall, there are 24 indeterminate samples out of 309 samples tested. Fifteen of the samples are below the determined cutoff value and nine were above. When the band patterns of the indeterminate samples were evaluated, it was recorded that NS3 band reactivity (12 samples) was the dominant pattern followed by C1 (5 samples), C2 (3 samples), NS4 (2 samples) and E2 (1 sample). All the indeterminate samples were PCR negative. Eight of these samples had follow up tests with either LIA or HCV RNA and all of them are either negative on the follow up HCV RNA test or no band change was recorded on LIA. Since all the HCV RNA results are negative, these results could correspond to individuals who had spontaneously eliminated the virus and who were in the seroreversion phase. The other possibility that must be considered is a false positive EIA result.

Some reports found good correlation between s/co ratio of anti-HCV and HCV viremia (13, 16, 24, 25, 26, 27). In a study conducted by Seo at al., anti-HCV s/co ratio accurately predicted the presence of viremia, with a cutoff value of 10.9 by Abbott 2nd generation anti-HCV assay (28). In another study that used Axsym HCV 3.0 (Abbott) as the screening test, 93.6% of the cases with a s/co>50 were HCV RNA positive (26). In the current study, the results obtained with the EIA test and PCR for HCV RNA were evaluated to find a possible relationship between the presence of virus genome and antibody response. It was recorded that the Architect s/co directly correlated with the presence of HCV RNA indicating viremia. HCV RNA positivity increased from 2.2% to 88.9% as the s/co value increased.

It is important for laboratories to determine a threshold point to distinguish between low and high positive anti-HCV result. The comparison between EIA and LIA test results indicate that a strong reactivity by screening assay predicts the positivity by the supplementary assay. With the architect anti-HCV assay (Abbott, Abbott Park, IL, USA), in those with s/co >3.27, only 11 (4.9%) samples are negative by LIA, so beyond that threshold, LIA does not add specificity to the screening EIA test. On the other hand, in those with low ratios, LIA testing is beneficial because of the high frequency of false positive results. Use of s/co ratios could help to choose the best strategy to use in a particular patient and minimize the amount of testing that needs to be performed while improving the reliability of the reported test result.

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