ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of the Signal-to-Cutoff Ratio of the Roche Elecsys HIV Ag/Ab Test for Predicting HIV-1 Infection in a Tertiary Care Hospital in Ankara, Türkiye

Ankara, Türkiye'deki Bir Üçüncü Basamak Hastanede HIV-1 Enfeksiyonunun Öngörülmesinde Roche Elecsys HIV Ag/Ab Testinin Sinyal/Kesim Oranının Değerlendirilmesi

Muhammed Furkan Kurkcu, Gizem Korkut, Ayfer Bakir

Department of Medical Microbiology, Health Sciences University, Etlik City Hospital, Ankara, Türkiye

ABSTRACT

Aim: *Accurate discrimination between true and false HIV reactivity is essential for timely diagnosis and avoiding unnecessary further testing. This study evaluated the diagnostic performance of the signal-to-cutoff (S/CO) ratio of a fourth-generation HIV Ag/Ab assay for predicting true HIV-1 infection.*

Materials and Methods: *A total of 715 reactive serum samples collected between January 2022 and December 2024 were analyzed. HIV screening was performed using a fourth-generation chemiluminescent microparticle immunoassay. Repeatedly reactive samples underwent confirmatory testing based on immunochromatographic principles. The optimal S/CO threshold for predicting true HIV infection was determined by ROC (Receiver Operating Characteristic) analysis.*

Results: *Out of 715 reactive samples, 309 (43.2%) were confirmed as true positives, while 406 (56.8%) were false positives. All false positives had S/CO values <100, and no true positives were identified among samples with S/CO <2.30. The median S/CO value for true positives was 738.0 (IQR: 239–1337), compared to 1.72 (IQR: 1.20–3.33) in false positives (p<0.001). Receiver operating characteristic analysis identified an optimal S/CO threshold of 29.7, which yielded an area under the curve of 0.997, with 97.1% sensitivity, 99.1% specificity, 91.6% positive predictive value, and 99.7% negative predictive value. The false-positive rate decreased from 56.8% at the ≥1.0 threshold to 1.3% at the ≥29.7 threshold.*

Conclusion: *The S/CO ratio in fourth-generation HIV Ag/Ab assays demonstrates high predictive accuracy for HIV infection. An S/CO threshold of ≥29.7 effectively reduces false-positive rates while maintaining diagnostic sensitivity, providing a valuable tool for clinical decision-making prior to confirmatory testing.*

Key words: *HIV; chemiluminescent microparticle immunoassay; sensitivity; specificity; ROC analysis*

ÖZET

Amaç: *HIV taramasında gerçek ve yanlış reaktiviteyi doğru şekilde ayırt edebilmek, zamanında tanı koymak ve gereksiz ileri tetkiklerin önüne geçmek açısından büyük önem taşır. Bu çalışmanın amacı, dördüncü nesil HIV Ag/Ab testinde sinyal/kesim oranının (S/CO) gerçek HIV-1 enfeksiyonunu öngörmedeki tanısal performansını değerlendirmektir.*

Materyal ve Metot: *Bu çalışmada, Ocak 2022 ile Aralık 2024 tarihleri arasında toplanan 715 reaktif serum örneği analiz edildi. HIV taraması, dördüncü nesil kemilüminesans mikropartikül immünoassay yöntemi ile gerçekleştirildi. Tekrarlayan reaktif bulunan örnekler, immünokromatografik prensiplere dayalı testlerle doğrulandı. Gerçek HIV enfeksiyonunu öngörmede en uygun S/CO eşik değeri, ROC analizi ile belirlendi.*

Bulgular: *715 reaktif örneğin 309'u (%43,2) doğrulanmış gerçek pozitif, 406'sı (%56,8) ise yanlış pozitif olarak değerlendirildi. Tüm yanlış pozitiflerin S/CO değeri <100 idi ve S/CO <2,30 olan örneklerde hiçbir gerçek pozitif saptanmadı. Gerçek pozitif örneklerde medyan S/CO değeri 738,0 (IQR: 239–1337), yanlış pozitiflerde ise 1,72 (IQR: 1,20–3,33) olarak bulundu (p<0,001). ROC (Receiver Operating Characteristic) analizine göre 29,7 S/CO eşik değeri en uygun eşik olarak belirlendi; bu noktada eğri altındaki alan (AUC) 0.997 olarak hesaplandı. Bu eşikte duyarlılık %97,1, özgüllük %99,1, pozitif prediktif değer %91,6 ve negatif prediktif değer %99,7 idi. Yanlış pozitiflik oranı, S/CO ≥1,0 eşiğinde %56,8 iken, ≥29,7 eşiğinde %1,3'e geriledi.*

Sonuç: *Dördüncü nesil HIV Ag/Ab testlerinde S/CO oranı, HIV enfeksiyonunu öngörmede yüksek doğruluk sağlamaktadır. ≥29,7 S/CO eşik değeri, tanısal duyarlılığı korurken yanlış pozitiflik oranını önemli ölçüde azaltarak, doğrulayıcı testler öncesinde klinik karar verme süreçlerinde faydalı bir araç sunmaktadır.*

Anahtar kelimeler: *HIV; kemilüminesans mikropartikül immünoassay; duyarlılık; özgüllük; ROC analizi*

İletişim/Contact: *Muhammed Furkan Kürkçü. Department of Medical Microbiology, Health Sciences University, Etlik City Hospital, Ankara, Türkiye* • ***Tel:*** *0 554 021 82 01* • ***E-mail:*** *furkan.kurkcu@gmail.com* • ***Geliş/Received:*** *18.06.2025* • ***Kabul/Accepted:*** *03.12.2025*

ORCID: *Muhammed Furkan Kürkçü: 0000-0002-7750-5002 • Gizem Korkut: 0009-0004-5891-5913 • Ayfer Bakır: 0000-0002-9006-5267*

Introduction

Human immunodeficiency virus (HIV), a *Lentivirus* in the Retroviridae family, remains a major global health concern, affecting approximately 39.9 million people worldwide (1,2). HIV-1 causes most AIDS cases, whereas HIV-2 mainly affects West Africa and accounts for about two million infections (3). Since the first reported HIV case in 1985, 40.480 HIV-positive individuals and 2.321 AIDS cases have been reported in Türkiye by the end of 2023. Despite rising diagnoses, Türkiye remains a low-prevalence country (4,5).

HIV-1/2 antigen/antibody combination immunoassays are widely used as initial screening tools. However, these tests are known to produce false-positive results, especially in populations with low HIV prevalence. To improve diagnostic accuracy, the Centers for Disease Control and Prevention (CDC) introduced a revised HIV testing algorithm in January 2019, aiming to maximize both sensitivity and specificity and to address discrepancies in test interpretations (6,7).

According to current guidelines, HIV screening should follow a stepwise approach, starting with a fourth-generation HIV-1/2 Ag/Ab immunoassay. If the result is reactive, an HIV-1/HIV-2 antibody differentiation test is conducted. The Geenius™ HIV-1/2 Supplemental Assay (Bio-Rad Laboratories, Redmond, USA) is the only FDA-approved test for this purpose. In cases where Geenius results are indeterminate or negative, HIV-1 nucleic acid testing (NAT) is required to confirm the diagnosis (7–9).

Serological assays based on enzyme immunoassay (EIA) technology remain the cornerstone of initial HIV testing (10). Fourth-generation EIA tests are particularly advantageous, as they enable the simultaneous detection of HIV p24 antigen and antibodies, thereby reducing the seroconversion window. Despite improvements in sensitivity, both third- and fourth-generation assays still carry a risk of false-positive outcomes, which affects test specificity (11–13).

False-positive HIV screening results may lead to significant emotional distress, especially during the waiting period for confirmatory testing (14). These inaccurate results may stem from technical issues such as sample mislabeling or biological causes such as autoimmune conditions or cross-reactivity with other infections. As such, confirmatory testing is essential to distinguish true HIV infection from false reactivity (7,15,16).

Rapid and accurate diagnosis of HIV remains crucial for preventing further transmission and ensuring timely clinical management. In light of increasing HIV screening efforts and the diagnostic challenges posed by false-positive results in low-prevalence settings, this study investigates the three-year prevalence data, evaluates the specificity performance of the Roche Elecsys HIV Ag/Ab Combo test, and proposes an optimized S/CO threshold to improve diagnostic accuracy.

Materials and Methods

Study Design

This study was conducted at Ankara Etlik City Hospital in Türkiye. Serum samples with reactive HIV screening results obtained between January 2022 and December 2024 were included. Initial screening and subsequent confirmatory test results were retrieved from laboratory records.

Diagnostic Procedure

Initial HIV screening was performed using a fourth-generation combination antigen/antibody assay based on the chemiluminescent microparticle immunoassay (CMIA) principle. This assay is designed to simultaneously detect HIV p24 antigen and antibodies to HIV-1 and HIV-2 in human serum and plasma.

Each sample's result is expressed as a signal-to-cutoff (S/CO) ratio. A value of S/CO ≥1.00 was interpreted as reactive, indicating presumptive HIV infection, whereas S/CO <1.00 was classified as non-reactive.

According to previously published validation studies, this assay demonstrates a sensitivity of 100% and a specificity of 99.87%.

All samples with reactive results were forwarded to the National HIV-AIDS Verification and Viral Hepatitis Reference Laboratory, operating under the General Directorate of Public Health, for confirmatory testing. There, samples were re-evaluated using a combination of confirmatory methods, including an enzyme-linked fluorescent assay (ELFA) that detects both HIV-1 p24 antigen and anti-HIV-1/2 antibodies, and an immunochromatographic confirmatory test to differentiate HIV-1 and HIV-2 infections.

In cases of indeterminate results or suspected acute HIV infection, HIV-1 RNA polymerase chain reaction (PCR) testing for active viremia and in-house proviral HIV-1 DNA PCR were performed for further

confirmation. HIV-1 RNA PCR was especially utilized for samples with non-reactive confirmatory serologic results to rule out early-phase infection.

To investigate the relationship between the S/CO ratio and confirmed HIV infection status, reactive screening samples were stratified into predefined S/CO intervals and analyzed in comparison with their final confirmed diagnostic outcome.

Ethics Approval

The study was approved by the Scientific Research Evaluation and Ethics Committee of Ankara Etlik City Hospital on August 28, 2024, with the approval number AEŞH-BADEK-2024-807.

Statistical Analysis

Data were analyzed using IBM Statistical Package for Social Sciences (SPSS) program version 25.0 (IBM Corp., USA). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test and visual inspection. As the S/CO values were non-normally distributed, they were presented as medians and interquartile ranges (IQRs) and compared using the Mann–Whitney U test. Categorical variables were compared using Pearson's chi-square test.

Final reference laboratory results were used as the reference standard. Receiver operating characteristic analysis assessed the ability of S/CO values to distinguish confirmed HIV-positive from non-confirmed samples and identify the optimal cutoff. Sensitivity, specificity, PPV, and NPV were calculated for selected thresholds. A p-value <0.05 was considered significant.

Table 1. *Distribution of true and false positive hıv screening results by signal-to-cutoff (S/CO) ıntervals and corresponding false positive rates*

S/CO interval	TP (n)	FP (n)	Total (n)	FPR (%)
1-5	2	338	340	99.4
>5-10	1	42	43	97.7
>10-50	11	25	36	69.4
>50-100	11	1	12	8.3
>100	284	0	284	0.0

TP: true positive; FP: false positive; FPR: false positive rate

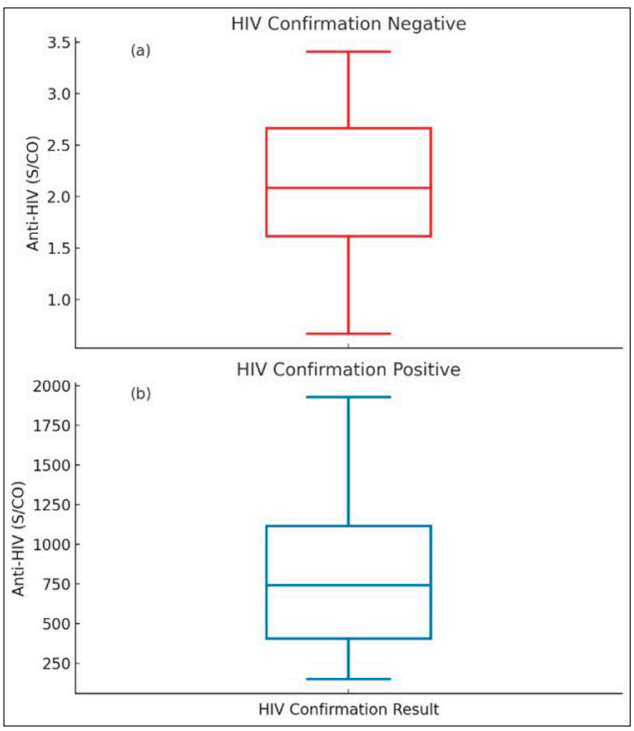

Figure 1. *Figure 1. Box-and-whisker plots of HIV Ag/Ab cutoff index values in the non-confirmed (a) and confirmed-positive (b) groups.*

Results

Distribution of Samples According to Test Results

A total of 715 anti-HIV reactive serum samples were analyzed. Of these, 309 samples (43.2%) were confirmed as HIV positive using an immunochromatographic confirmatory test, while 406 samples (56.8%) were classified as false positives. Notably, all false-positive results were detected in samples with an S/CO value below 100.

In our study, the highest false-positive rate (99.4%) was observed in samples with S/CO values between 1 and 5. No true positive cases were identified among samples with S/CO values below 2.3. Conversely, no false-negative cases were observed among samples with S/CO values above 100, meaning no HIV-infected individuals were missed in this group (Table 1).

The median S/CO value for true positive samples (n=309) was 738 (IQR [interquartile range]=239–1337), whereas the median S/CO value for false positive samples (n=406) was 1.72 (IQR=1.20–3.33). This difference was statistically significant (p<0.001) (Fig. 1).

The optimal S/CO threshold for detecting HIV infection using the Roche Elecsys assay was determined to be 29.7, at which point the area under the ROC curve (AUC) reached its maximum value of 0.997 (Fig. 2). At this threshold, the false-positive rate was reduced to

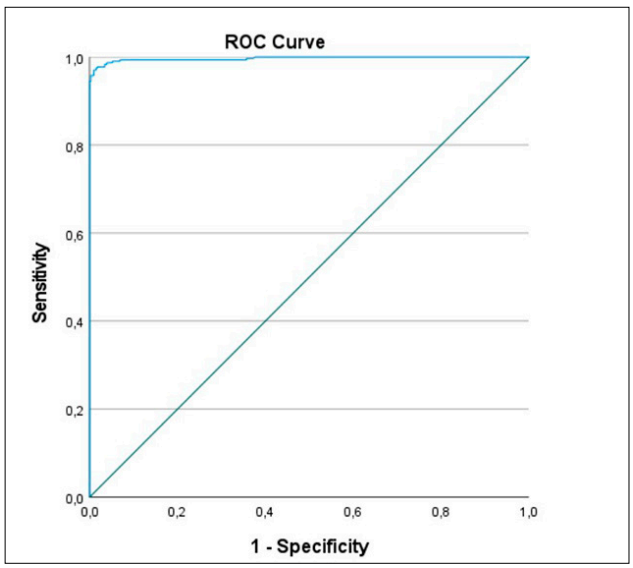

Figure 2. *Performance of the Roche Elecsys sample-to-cut-off for detecting HIV cases with ROC curve analysis.*

1.96%. An S/CO value of ≥29.7 yielded a sensitivity of 97.1%, specificity of 99.1%, PPV of 91.6%, and NPV of 99.7%. In contrast, the false-positive rate observed at the standard threshold of S/CO ≥1.0 was 56.8%, which decreased markedly to 1.96% when applying the optimized threshold of S/CO ≥29.7.

The performance outcomes of the Roche Cobas HIV Ag/Ab Combo Test across different S/CO value intervals are presented in Table 2.

Table 2. *Performance of the Roche Elecsys HIV Ag/Ab Combo Assay according to S/CO ratios*

	S/CO[§]					
	≥1	≥5	≥10	≥29.7	≥50	≥100
False positive (n)	406	61	24	4	1	0
True positive (n)	309	306	305	299	294	283
Sensitivity (%)	*	99	98.7	97.1	95.1	91.6
Specificity (%)	*	85	94.1	99.9	99.8	100
PPV (%)	*	83.4	92.7	91.6	99.7	100
NPV (%)	*	99.1	99.0	99.7	96.4	94.0

[§]S/CO: Sample signal/cut-off, n: number; PPV: positive predictive value, NPV: negative predictive value. * Since confirmatory testing was not performed on HIV Ag/Ab negative samples, this value could not be calculated.

Discussion

Early HIV diagnosis enables timely prevention of transmission and initiation of antiretroviral therapy (ART) (17). Fourth-generation HIV-1/2 Ag/Ab assays are recommended for initial screening (9). However, diagnostic accuracy is essential because HIV misdiagnosis may have important psychological and social consequences (18). HIV diagnosis requires at least two reactive tests, or three separate tests in populations with an HIV prevalence <5% (19). Although fourth-generation assays are widely used for HIV screening in Türkiye, confirmatory testing and nucleic acid testing (NAT) are performed only at Ministry of Health–authorized centers. Despite their high specificity, EIA-based assays may have low PPVs in low-prevalence settings, making false-reactive results clinically relevant (20–28). Systemic infections, vaccination, malignancy, and molecular mimicry may contribute to false reactivity (29–31).

In this cohort, HIV infection was confirmed in 309 of 715 reactive samples (43.2%), whereas 406 (56.8%) were non-confirmed. All non-confirmed samples had S/CO values <100, while no confirmed-positive sample had an S/CO value <2.3. This high proportion of non-confirmed reactivity is consistent with reported false-positive rates of 39.5%–69.8% in low-prevalence settings (24–26).

In our study, false-positive rates were highest at low S/CO values: 99.4% (338/340) for S/CO 1–5 and 97.7% (42/43) for S/CO >5–10. Similarly, Zucker et al. reported a 90% false-positive rate at S/CO 1–10, whereas all patients with S/CO >38.78 were confirmed positive (32). These findings support the potential use of assay-specific S/CO values for risk stratification of reactive HIV screening results, particularly in populations or clinical settings in which false reactivity may be more frequent, such as pregnancy or immune-mediated disorders.

Xia et al. analyzed over 150.000 samples using the *Elecsys® HIV combi PT* assay, the same testing platform used in our study. They reported a mean S/CO value of 643.5 for confirmed positive cases and 3.17 for false-positive cases. Notably, no false positives were observed in samples with a COI value ≥37.75, highlighting the strong predictive value of high S/CO ratios for diagnostic accuracy and supporting the reliability of this testing system (33).

In our study, the median S/CO value was 738 for 309 true-positive samples, whereas it was 1.72 for 406 false-positive samples. This difference was statistically significant. Moreover, no true-positive cases were identified in samples with an S/CO value below 2.30, yielding a negative predictive value (NPV) of 100%. Similarly, White et al. reported median S/CO values of 539.2 and 1.93 for HIV-positive and HIV-negative samples,

respectively (p<0.001), with an NPV of 100% for samples with an S/CO <1.58 (34).

Similarly, Yaman et al. found no HIV-1 infection in samples with S/CO <3.05, whereas all samples with S/CO ≥7.20 were confirmed by line immunoassay or molecular testing; this threshold yielded 100% sensitivity, 95% specificity, 97% PPV, and 100% NPV (35). Together, these findings support assay-specific S/CO thresholds for risk stratification in low-prevalence settings and may reduce unnecessary confirmatory testing.

In low-prevalence populations, the PPV of EIA-based HIV screening has been reported as 71%–83% (36). In our study, the Roche Elecsys HIV Ag/Ab Combo assay showed high diagnostic performance at an S/CO threshold of 29.7, with a sensitivity of 97.1% and specificity of 99.1%. However, optimal S/CO thresholds vary across studies, ranging from 3.78 to 32.7 (24–26,37). Therefore, S/CO values may help estimate the likelihood of true HIV positivity and prioritize reactive samples, but should not replace confirmatory testing.

This study has some limitations. The fourth-generation test used in this study does not differentiate between p24 antigen and antibodies. The use of a fifth-generation test, which can make this distinction, could have provided more detailed diagnostic insights. Additionally, as this was a retrospective study, patient data on risk behaviors and comorbidities were unavailable. Lastly, in samples from individuals in the acute or very early stage of HIV infection, true-positive cases may have been missed due to low S/CO values.

In conclusion, when the S/CO threshold was increased from 1 to 29.7, the false-positive rate significantly decreased from 56.8% to 1.3%. A higher S/CO threshold, such as 100, could further reduce false-positive results; however, it may also compromise test sensitivity and increase the risk of false-negative outcomes. In resource-limited settings where confirmatory testing is not readily available, S/CO thresholds may serve as a valuable surrogate marker for estimating the likelihood of true positivity. Early identification of HIV-infected individuals remains critical for preventing further transmission and ensuring effective clinical management.

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