Research Square

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Epidemiological Characteristics of HTLV Infection and Evaluation of ELISA Screening Performance Among Hospital-Based Populations in Ningde, China

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Research Article

Keywords: HTLV, enzyme-linked immunosorbent assay, real-time quantitative PCR, infection rate, Ningde City

Posted Date: July 27th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10321845/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Ningde City, Fujian Province, China, has the highest reported prevalence of human T-cell lymphotropic virus (HTLV) infection in the country. Nevertheless, epidemiological data on HTLV infection and the screening performance of enzyme-linked immunosorbent assay (ELISA) in general hospital-based populations in this region remain scarce.

Methods

A total of 11,788 samples were collected from outpatients, inpatients, and physical examination (PE) participants at Ningde Municipal Hospital between 2019 and 2024. ELISA was used for primary screening. All 153 ELISA-reactive samples and a preferentially selected subset of 487 ELISA-non-reactive samples (prioritizing those with higher S/CO ratios) subsequently underwent confirmatory real-time quantitative PCR. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of ELISA were calculated using PCR as the reference standard. Binary logistic regression was performed to identify factors associated with HTLV seropositivity.

Results

The overall ELISA initial reactive rate was 1.30% (153/11,788). The reactive rate among outpatients and inpatients (1.60%) was significantly higher than that among PE participants (0.46%) ($P < 0.001$). Female sex, older age, and outpatient/inpatient status were independently associated with seropositivity. The overall sensitivity and specificity of ELISA were 91.49% and 95.19%, respectively. ROC analysis identified an optimal cut-off value of S/CO = 0.3164, yielding an AUC of 0.9642.

Conclusions

HTLV infection prevalence is relatively high in Ningde, particularly among clinical patients. Although ELISA demonstrated acceptable overall screening performance—though true sensitivity may be marginally underestimated due to the verification strategy employed—subgroup differences in diagnostic accuracy underscore the need for PCR confirmation and population-specific cut-off optimization, especially in high-endemic settings.

1. Introduction

Human T-cell lymphotropic virus (HTLV) is a human retrovirus capable of establishing lifelong persistent infection, transmitted primarily through blood transfusion, mother-to-child transmission, and sexual contact[1].HTLV-1, the most prevalent subtype, is the established causative agent of adult T-cell

leukemia/lymphoma (ATL)[2]and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)[3].HTLV-2 is predominantly found among people who inject drugs (PWID) in North America and Europe, as well as among indigenous populations in the Americas and Africa[4].In China, HTLV-1 is the predominant subtype, whereas HTLV-2 infection remains rare and has not been systematically characterized[5].Owing to its prolonged latency period and largely asymptomatic carrier state, HTLV facilitates covert transmission within communities [6].

Current detection approaches include serological assays—such as enzyme-linked immunosorbent assay (ELISA) and chemiluminescence immunoassay (CMIA) — for initial screening[7, 8],followed by confirmatory methods such as Western blot[9]or polymerase chain reaction (PCR) for nucleic acid detection[10].

ELISA is widely employed in blood donor screening owing to its operational simplicity, cost-effectiveness, and relatively high sensitivity and specificity[11, 12].Although recent studies have evaluated its performance in Chinese hospital settings, these investigations predominantly enrolled suspected HTLV-infected individuals, whose infection risk and demographic profiles differ substantially from those of general outpatient or PE populations — thereby limiting the generalizability of findings to routine clinical screening scenarios[13].Furthermore, most previous studies based on blood donor cohorts applied partial verification strategies, confirming only ELISA-reactive samples by PCR or Western blot while leaving ELISA-non-reactive samples unverified — a practice known as partial verification bias that may distort estimates of sensitivity and specificity[14, 15].Ningde City, located in southeastern Fujian Province, China, has been identified as the region with the highest HTLV prevalence in the country[5, 16].The relatively elevated proportion of seropositive specimens in this setting provides an ideal context for rigorously evaluating ELISA performance in a high-endemic hospital-based population. Nevertheless, data on HTLV prevalence and ELISA diagnostic accuracy among general medical and PE populations in this area remain scarce.

To address these knowledge gaps, the present study was designed to investigate the epidemiological characteristics of HTLV infection and to systematically evaluate the diagnostic performance of ELISA screening in hospital-based outpatient, inpatient, and PE populations in Ningde City. To the best of our knowledge, this is among the first studies to: (1) evaluate ELISA screening performance concurrently across general outpatient, inpatient, and physical examination populations in a high-endemic region of China; (2) mitigate partial verification bias — a common methodological limitation in prior HTLV ELISA studies based on blood donor cohorts — by confirming both all ELISA-reactive specimens and selected subset of ELISA-non-reactive specimens by PCR in a hospital-based setting; and (3) derive population-specific optimal ELISA cut-off values through ROC analysis for distinct hospital subgroups, thereby providing actionable screening thresholds for clinical practice.

2. Materials and Methods

2.1 Study Population

A total of 11,788 participants were enrolled, comprising outpatients, inpatients, and physical examination (PE) individuals who attended Ningde Municipal Hospital between 2019 and 2024.The median age of participants was 46 years (IQR: 31.08–59.92). This study was approved by the Ethics Committee of Ningde Municipal Hospital (approval number: NSYKYLL-2022-1015), and the requirement for informed consent was waived due to the retrospective and observational nature of the study.All personal data pertaining to study participants were handled in strict confidence.

2.2 Reagents and Instruments

2.2.1 Reagents

The HTLV-I/II antibody detection kit (double-antigen sandwich ELISA format), HTLV-I nucleic acid detection kit (fluorescent probe-based PCR method), and DNA/RNA extraction kit (magnetic bead-based method) were all supplied by Beijing Wantai Biological Pharmacy Co., Ltd. (Beijing, China).

2.2.2 Instruments

The following instruments were used in this study: a Zhengzhou Antu microplate reader (model PHPMO; Zhengzhou Antu Bioengineering Co., Ltd., China), a Yuandian semi-automatic nucleic acid extractor (model SLA-32; Yuandian Biotechnology Co., Ltd., Taiwan, China), a CFX96 real-time PCR system (Bio-Rad Laboratories, Hercules, CA, USA), and an ABI 3730XL DNA sequencer (Applied Biosystems, Foster City, CA, USA).2.3 Methods

2.3.1 ELISA Screening

All specimens were tested for HTLV-I/II antibodies using the Beijing Wantai double-antigen sandwich ELISA kit. Specimens yielding a reactive result on initial screening were retested in duplicate. Those remaining reactive upon repeat testing were designated as ELISA-reactive (i.e., initial screen-positive).

2.3.2 Real-Time Quantitative PCR Confirmation

All 153 ELISA-reactive specimens underwent confirmatory real-time quantitative PCR using the Beijing Wantai HTLV-I nucleic acid detection kit (fluorescent probe method)..Among ELISA non-reactive specimens, a subset of 487 samples were selected for PCR confirmation, with priority given to specimens exhibiting higher S/CO ratios (i.e., those approaching the manufacturer's cut-off threshold of 1.0). This near-cutoff enriched verification strategy was adopted to maximize the detection of potential false-negative cases; however, it does not constitute a random or representative sample of all ELISA non-reactive specimens.

2.4 Statistical Analysis

All statistical analyses were performed using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). Categorical variables were compared using the chi-square (χ^2) test. Normally distributed continuous variables were expressed as mean ± standard deviation (SD) and compared using the independent samples t-test. Non-normally distributed continuous variables were expressed as median (P25, P75) and

compared using the Wilcoxon rank-sum test. Multivariable binary logistic regression was performed to identify independent factors associated with HTLV seropositivity, with adjustment for potential confounders. Receiver operating characteristic (ROC) curve analysis was conducted to determine the optimal screening cut-off value. A two-sided P-value of less than 0.05 was considered statistically significant.

3. Results

3.1 General Characteristics

Of the 11,788 specimens tested, 153 were ELISA-reactive, yielding an overall initial reactive rate of 1.30%. The reactive rate increased progressively with age, ranging from 0.56% in participants aged < 40 years to 2.44% in those aged ≥ 60 years (χ^2 = 49.631, P < 0.001). The difference in reactive rates between males (1.08%) and females (1.48%) did not reach statistical significance (χ^2 = 3.646, P = 0.056). Detailed characteristics are presented in Table 1.

Table 1
General Characteristics and HTLV Seropositivity by Subgroup

Variable	Category	Reactive Rate	χ^2	*P*
Sex	Male	1.08%	3.646	0.056
	Female	1.48%		
Age group	< 40 years	0.56%	49.631	< 0.001
	≥ 40–<60 years	1.30%		
	> 60 years	2.44%		

3.2 Comparison of Baseline Characteristics and ELISA Results Between Population Groups

Compared with the PE group, the outpatient/inpatient group was significantly older (median age: 46.00 vs. 38.71 years, Z = 21.025, P < 0.001) and had a higher proportion of female participants (57.0% vs. 44.7%, χ^2 = 136.182, P < 0.001). The ELISA reactive rate in the outpatient/inpatient group (1.60%, 139/8,740) was significantly higher than that in the PE group (0.46%, 14/3,048) (χ^2 = 22.568, P < 0.001). Detailed results are summarized in Table 2.

Table 2
Comparison of Baseline Characteristics and HTLV Reactive Rates Between Population Groups

PE group	Sex (Male/Female)	Age (years)	Reactive Rate
	1,685/1,363	**38.71(29.17, 52.00)**	**0.46%**
Outpatient/inpatient group	3,762/4,978	46.00(31.08, 59.92)	1.60%
Statistical value(χ^2/*Z*)	136.182	21.025	22.568
P value	< 0.001	< 0.001	< 0.001

3.3 Logistic Regression Analysis of Factors Associated with HTLV Seropositivity

After adjustment for potential confounders, three independent risk factors for HTLV seropositivity were identified: outpatient/inpatient status (*OR* = 2.51, 95% *CI*: 1.48–4.59, *P* = 0.001), female sex (*OR* = 1.60, 95% *CI*: 1.15–2.25, *P* < 0.001), and older age (*OR* = 1.03 per year increase, 95% *CI*: 1.02–1.04, *P* < 0.001). Detailed results are presented in Table 3.

Table 3
Multivariable Logistic Regression Analysis of Factors Associated with HTLV Seropositivity

Factor	*β*	*SE*	*z*	*P*	*OR(95%CI)*
Population group: outpatient/inpatient vs. PE	0.919	0.287	3.207	0.001	2.51(1.48–4.59)
Sex: female vs. male	0.469	0.171	2.735	< 0.001	1.60(1.15–2.25)
Age (per year)	0.032	0.005	6.562	< 0.001	1.03(1.02–1.04)

3.4 Evaluation of ELISA Screening Performance

A total of 640 specimens were concurrently evaluated by both ELISA and PCR. Using PCR as the reference standard, 141 specimens were confirmed PCR-positive. Overall, ELISA demonstrated a sensitivity of 91.49% (95% *CI*: 85.71%–95.06%), specificity of 95.19% (95% *CI*: 92.94%–96.75%), PPV of 84.31% (95% *CI*: 77.71%–89.22%), and NPV of 97.53% (95% *CI*: 95.74%–98.58%).

Stratified analysis revealed notable differences in diagnostic performance between population subgroups. In the outpatient/inpatient group, sensitivity was higher (95.08%) but specificity was lower (91.42%) compared to overall estimates, suggesting an elevated risk of false-positive results in this clinical population. In contrast, the PE group exhibited markedly lower sensitivity (68.42%; 95% *CI*: 46.02%–84.64%) despite near-perfect specificity (99.57%), indicating a potential risk of missed diagnoses in this lower-prevalence population. Complete diagnostic performance metrics are summarized in Table 4.

Table 4
Comparison of ELISA Performance for HTLV Detection Across Population Groups

Group		PCR+	PCR-	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Overall	ELISA+	129	24	91.49 (85.71–95.06)	95.19 (92.94–96.75)	84.31 (77.71–89.22)	97.53 (95.74–98.58)
	ELISA-	12	475				
Outpatient/inpatient	ELISA+	116	23	95.08 (89.69–97.73)	91.42 (87.45–94.21)	83.45 (76.39–88.71)	97.60 (94.88–98.90)
	ELISA-	6	245				
PE	ELISA+	13	1	68.42 (46.02–84.64)	99.57 (97.59–99.92)	92.86 (68.53–98.73)	97.46 (94.56–98.83)
	ELISA-	6	230				

3.5 ROC Curve Analysis and Optimal Cut-Off Determination

ROC curve analysis of ELISA S/CO values demonstrated strong overall discriminatory performance, with an AUC of 0.9642 (95% *CI*: 0.9436–0.9848) (Fig. 1). The optimal cut-off for the overall population was determined to be S/CO = 0.3164 (sensitivity: 96.5%, specificity: 95.2%, Youden index: 0.9164). Subgroup analysis yielded an identical optimal cut-off for the outpatient/inpatient group (S/CO = 0.3164; AUC: 0.9601, Youden index: 0.8896), and a marginally higher threshold for the PE group (S/CO = 0.3506; AUC: 0.9329, Youden index: 0.8904). Notably, all derived optimal cut-off values were substantially lower than the manufacturer's recommended threshold of S/CO = 1.0.

4. Discussion

HTLV infection remains a neglected public health concern worldwide. In China, Fujian Province is recognized as a high-endemic region, with Ningde City exhibiting particularly elevated infection levels. In the present study, the overall ELISA reactive rate was 1.30%, comparable to that reported in Vitória, Brazil[17]. Previous data from blood donors in Ningde reported an ELISA reactive rate of 0.39%[18], while the PE group in the current study yielded a rate of 0.46%, marginally higher than that observed in blood donors. In contrast, the outpatient/inpatient group demonstrated a substantially higher reactive rate of 1.60%, exceeding those of both the blood donor and PE populations. These disparities likely reflect differences in population composition: blood donors and PE individuals predominantly represent relatively healthy subjects, whereas outpatients and inpatients tend to have a higher burden of underlying disease. Although the majority of HTLV-1-infected individuals remain asymptomatic carriers, the virus can perturb immune regulation and precipitate a range of pathological sequelae, including polymyositis, arthropathy, Sjögren's syndrome, and infective dermatitis, as well as more severe outcomes such as ATL and HAM/TSP[19, 20]. Collectively, these findings suggest that prevalence estimates derived exclusively from blood donor cohorts may substantially underestimate the true burden of HTLV infection in Ningde. The higher infection rate observed among clinical patients indicates that the public health impact of

HTLV in this region may be more considerable than previously recognized, underscoring the need for targeted screening and confirmatory testing in high-risk populations.

Logistic regression analysis identified outpatient/inpatient status, female sex, and older age as independent risk factors for HTLV seropositivity. The risk of HTLV infection among outpatients and inpatients was 2.51-fold that of PE individuals, consistent with the elevated disease burden characteristic of clinical populations. The observed higher seropositivity risk among females (*OR* = 1.60) is concordant with findings from previous studies[21, 22], although the underlying biological mechanisms remain to be fully elucidated. Older age was also confirmed as an independent risk factor, in agreement with prior reports[17, 23]. Several mechanisms may account for this association. First, the prolonged latency of HTLV infection implies that older individuals have accumulated greater cumulative exposure across multiple transmission routes over their lifetime. Second, immune senescence associated with aging may increase susceptibility to viral persistence. Third, older cohorts may have received blood transfusions prior to the nationwide implementation of routine HTLV donor screening in China. Finally, in earlier eras when breastfeeding was more prevalent, mother-to-child transmission may have contributed more substantially to cumulative infection risk in this high-endemic region. Nevertheless, the cross-sectional design of the present study precludes full disentanglement of age effects from birth cohort effects, and prospective cohort studies are warranted to clarify this relationship.

The overall ELISA performance in the present study was satisfactory, broadly meeting the requirements for routine clinical screening. By comparison, some prior investigations have reported markedly lower PPVs; for example, Chen et al.[24] reported a PPV of 3.66% in Jiangsu Province, and Liao et al.[25] reported a PPV of 5.26% in Guangdong Province. These discrepancies are largely attributable to differences in background HTLV prevalence across study settings. The reactive rate in the present cohort (1.30%) substantially exceeded those reported in Jiangsu (0.002%) and Guangdong (0.034%), reflecting the markedly higher endemic level in Ningde. As is well established, PPV is strongly influenced by background prevalence; even assays with high sensitivity and specificity will yield low PPVs in low-prevalence settings. Accordingly, in regions with low HTLV endemicity, ELISA-reactive results should be interpreted with caution and verified by PCR or other confirmatory methods[26].

Stratified analysis revealed that ELISA sensitivity in the outpatient/inpatient group (95.08%) exceeded the overall estimate, suggesting robust case-detection capacity in this clinical population. The NPV of 97.60% in this group indicates that ELISA-negative results carry substantial value for excluding infection. However, specificity in the outpatient/inpatient group (91.42%) was lower than in the PE group, implying a non-negligible rate of false-positive results. This may be attributable to immune dysregulation, systemic inflammation, or other pathological states prevalent in clinical patients, which can heighten non-specific reactivity. Conversely, ELISA sensitivity in the PE group was considerably lower (68.42%; 95% CI: 46.02%–84.64%), raising concerns regarding missed diagnoses. It should be noted, however, that only 19 PCR-confirmed positive cases were identified in the PE group, yielding wide confidence

intervals for sensitivity and PPV estimates; these findings therefore warrant validation in larger PE cohorts before definitive conclusions can be drawn.

Failure to optimize the ELISA cut-off value for specific populations may result in a suboptimal balance between false-positive and false-negative rates. For instance, in a low-prevalence setting in London, raising the cut-off threshold to S/CO > 20 reduced the false-positive rate from 57% to 5%, illustrating the utility of population-specific cut-off adjustment in low-endemic regions[27]. In the present study, ROC analysis using the maximum Youden index criterion identified optimal cut-off values of S/CO = 0.3164 for both the overall and outpatient/inpatient populations (Youden indices: 0.9164 and 0.8896, respectively), and S/CO = 0.3506 for the PE population (Youden index: 0.8904)—all substantially lower than the manufacturer's default threshold of S/CO = 1.0. Notably, specimens with S/CO values between 0.32 and 1.0 were exceedingly rare in the present cohort, such that the derived optimal thresholds and the manufacturer's default cut-off yielded virtually identical classification outcomes in practice. These findings suggest that in high-endemic regions such as Ningde, lowering the cut-off threshold may improve sensitivity while preserving acceptable specificity, and that population-tailored threshold adjustment could meaningfully optimize overall screening performance in clinical practice. This recommendation stands in directional contrast to the strategy of raising cut-off values to reduce false positives in low-endemic settings, thereby underscoring the critical influence of background prevalence on optimal threshold determination. The modest difference in optimal cut-off values between the two subgroups (outpatient/inpatient: 0.3164 vs. PE: 0.3506) reflects differences in true infection rates, underlying disease status, and immunological backgrounds. In the PE group, the slightly higher optimal cut-off supports the application of a more conservative threshold in lower-risk, healthy populations to minimize false-positive results. Conversely, the lower optimal cut-off in the outpatient/inpatient group reflects the clinical imperative to maximize sensitivity and reduce the risk of missed diagnoses in higher-risk populations.

Several limitations of the present study merit acknowledgment. First, this was a single-center, cross-sectional study conducted at a single hospital in Ningde, which limits the generalizability of findings to other settings and precludes differentiation between age effects and birth cohort effects; multicenter prospective studies are warranted for further validation. Second, PCR confirmation was performed on a selected subset of 487 ELISA non-reactive specimens, with priority given to those with higher S/CO values approaching the manufacturer's cut-off. This near-cutoff enriched verification strategy, while clinically motivated to capture potential false-negative cases, introduces partial verification bias: because specimens with lower S/CO values—which are less likely to be true positives—were systematically underrepresented in the verification subset, the estimated sensitivity and NPV are likely underestimated relative to their true values. Third, the ELISA reagent used in this study detects antibodies against both HTLV-1 and HTLV-2, whereas the PCR assay targets HTLV-1 exclusively; this discordance in detection scope could theoretically lead to the misclassification of HTLV-2-infected individuals as PCR-negative false positives, potentially inflating false-positive counts and affecting estimates of specificity and PPV. However, HTLV-2 infection is exceedingly rare in China—a nationwide seroprevalence survey among blood donors by Chang et al.[5]identified no HTLV-2 infections among all

confirmed-positive specimens—suggesting that the practical impact of this discordance on the primary conclusions of the present study is likely minimal.

5. Conclusions

HTLV infection prevalence is relatively high among hospital-based outpatients, inpatients, and PE populations in Ningde City, with female sex, advanced age, and outpatient/inpatient status identified as independent risk factors for seropositivity. ELISA demonstrated acceptable overall screening performance and can fulfill basic clinical screening requirements; however, diagnostic performance varied considerably across population subgroups. In the outpatient/inpatient group, a non-negligible risk of false-positive results was observed, whereas in the PE group, a risk of missed diagnoses was identified. These findings underscore the importance of targeted HTLV screening in high-endemic regions, in conjunction with PCR or other confirmatory assays to improve overall diagnostic accuracy. Furthermore, population-specific optimization of ELISA cut-off values warrants consideration to achieve a more favorable balance between sensitivity and specificity across different clinical contexts.

Abbreviations

ATL Adult T-cell leukemia/lymphoma

AUC Area under the curve

CI Confidence interval

CMIA Chemiluminescence immunoassay

ELISA Enzyme-linked immunosorbent assay

HAM/TSP HTLV-1-associated myelopathy/tropical spastic paraparesis

HTLV Human T-cell lymphotropic virus

HTLV-1 Human T-cell lymphotropic virus type 1

HTLV-2 Human T-cell lymphotropic virus type 2

NPV Negative predictive value

PE Physical examination

PPV Positive predictive value

PWID People who inject drugs

ROC Receiver operating characteristic

S/CO Signal-to-cutoff ratio

PCR Polymerase chain reaction

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of Ningde Municipal Hospital (Approval No.: [NSYKYLL-2022-1015]). The study utilized residual serum samples remaining after routine clinical laboratory testing, with no additional samples collected specifically for research purposes. All samples and associated data were anonymized prior to analysis. Given the retrospective nature of the study, the use of leftover clinical specimens, the minimal risk to participants, and the impracticability of obtaining individual consent, the requirement for informed consent was waived by the Ethics Committee.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests

Funding

This research was supported by the Ningde City Natural Science Foundation Joint Project, Fujian Province, China (No. 2022J03).

Authors' contributions

Wenqiang Wang performed the experiments, collected and analyzed the data, and drafted the manuscript. Zuodong Ye assisted with data collection and statistical analysis. Fenrui Fu assisted with sample processing and data interpretation. Yuying Qi and Renqing Ye conceived and designed the study, supervised the research, provided critical revision of the manuscript for important intellectual content, and are responsible for the overall content as guarantors. Yuying Qi and Renqing Ye are the corresponding authors. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

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Figures

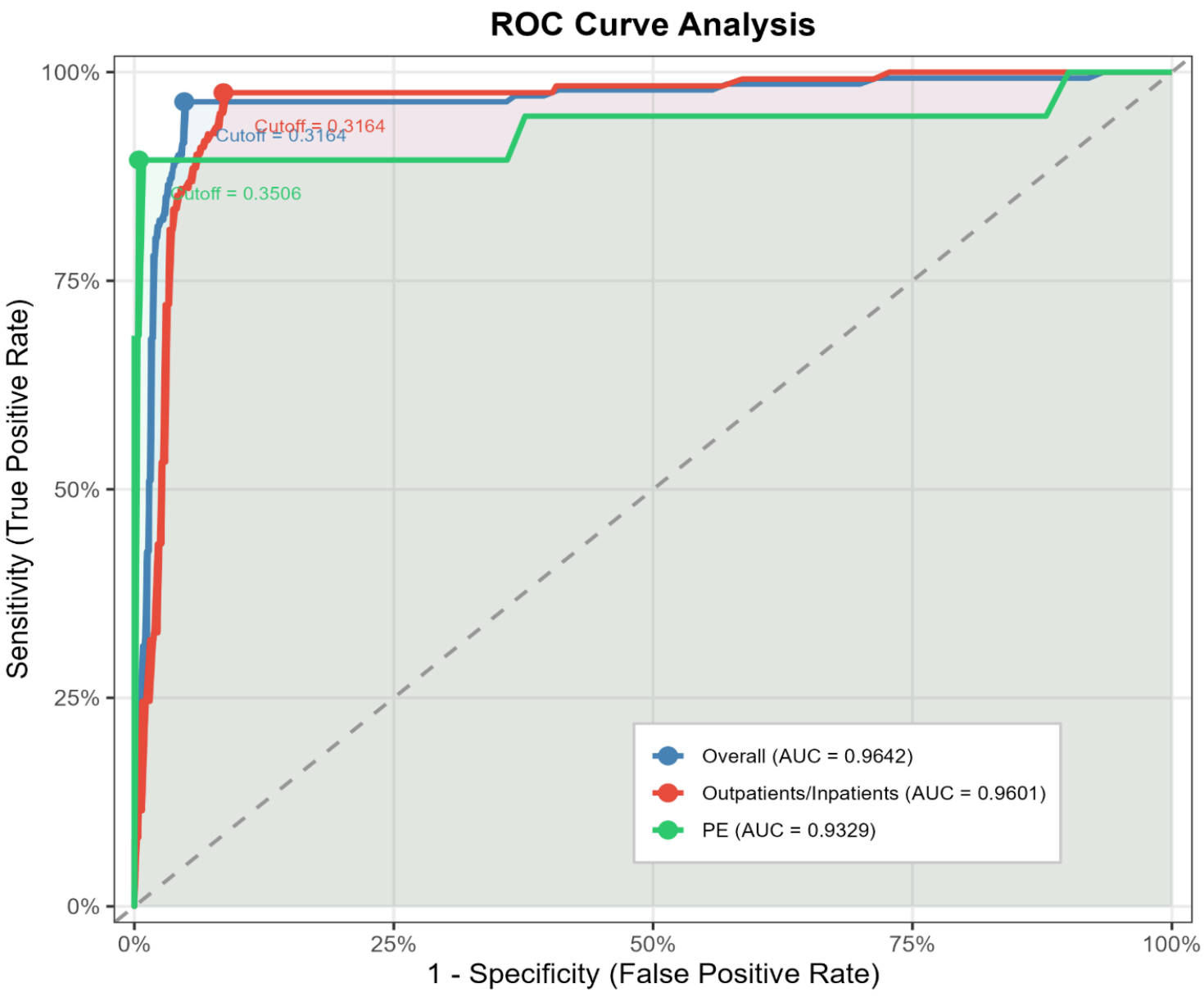


Figure 1

ROC curves of ELISA S/CO values for HTLV detection in the overall, outpatient/inpatient, and PE.