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ORIGINAL ARTICLE

Comparison of Diagnostic Algorithms with Commercial Kits Used to Detect Syphilis Antibodies

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SUMMARY

Background: **Nowadays, especially in laboratories with high testing capacity, the widespread use of automated treponemal tests has increased the importance of algorithms used for syphilis serodiagnosis. In suspected syphilis cases, choosing the best algorithm is important from the aspect of diagnosis, treatment initiation, and treatment follow-up. In this study, we aimed to compare the diagnostic performance of traditional, reverse, and European Center for Disease Prevention and Control (ECDC) algorithms according to the clinical diagnosis of syphilis using rapid plasma reagin (RPR), chemiluminescence immunoassay (CLIA), and *Treponema pallidum* hemagglutination (TPHA) tests.**

Methods: **Between March 2023 and July 2023, a total of 297 patients from various units of our hospital, suspected of having syphilis, were included in the study. All samples were analyzed using RPR, CLIA, and TPHA tests, and three different algorithms were examined separately. Clinical diagnosis was considered the gold standard.**

Results: **A total of 105 patients have been diagnosed with syphilis. When the patients' clinical diagnosis were used as a reference, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the traditional algorithm were found to be 41.9%, 100%, 100% and 75.9%, respectively, and all these parameters were found to be 100% for the reverse and ECDC algorithms. Moderate agreement (kappa value 0.483, $p < 0.001$) was found between the traditional and reverse algorithms. Very good agreement (kappa value 1.0, $p < 0.001$) was found between ECDC and the reverse algorithm.**

Conclusions: **In diagnosing suspected syphilis cases, the reverse algorithm and ECDC algorithms utilizing treponemal tests as the initial step were found to be superior to the traditional algorithm. Our study demonstrates that treponemal antibody tests are superior when employed as the initial step in diagnosing syphilis in patients with latent syphilis among suspected cases. Nontreponemal tests should be used solely to evaluate disease activity and response to therapy.**

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KEYWORDS

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INTRODUCTION

Syphilis is a systemic infectious disease caused by *Treponema pallidum* that can affect the skin, mucosa, and internal organs. It is usually transmitted sexually [1]. It was first seen among French soldiers in 1495 and was given the name "syphilis" [2]. Syphilis is a common

health problem worldwide, especially in developing countries. The World Health Organization (WHO) reported that there were 19.9 million individuals aged 15 - 49 years infected with syphilis worldwide, 6.3 million of which were new cases. It has been reported that it is transmitted through heterosexual intercourse in underdeveloped countries and male-to-male intercourse in developed countries [3]. The variability of clinical signs and symptoms, the variety of complications that can be seen years later in untreated individuals, and the problems in interpreting serological tests cause difficulties and delays in the diagnosis of syphilis [4]. *Treponema pallidum* can only be cultured *in vivo* and cannot be examined with simple laboratory stains. It is unlikely that new molecular tests for syphilis will replace serology in the short term. Therefore, serological tests are widely used to diagnose syphilis and monitor treatments. [5]. Syphilis serological tests are divided into two types: nontreponemal and treponemal tests. Nontreponemal tests include the Venereal Disease Research Laboratories (VDRL), RPR, and toluidine red unheated serum test [6]. These tests detect antibodies against lipoidal antigens during early and active infections. Non-treponemal testing can also be used to monitor disease activity and the effectiveness of the treatment. In contrast, treponemal tests can detect antibodies to treponemal antigens such as Tp15, Tp17, Tp45, and Tp47. *Treponema pallidum* hemagglutination test, *T. pallidum* particle agglutination (TPPA) test, fluorescent treponemal antibody absorption (FTA-ABS) test, *T. pallidum* IgG immunoblot test, enzyme immunoassay (EIA), CLIA, and electrochemiluminescence immunoassay (ECLIA) are some of the available treponemal tests. It is not sufficient to rely on a single serological test for the diagnosis of syphilis. Therefore, a combination of serological tests is used according to a specific sequence of methods called an algorithm for diagnosing syphilis. Three algorithms are recommended for diagnosing syphilis serologically. The traditional algorithm is designed to detect active infection, with the first step involving a non-treponemal test and confirmation using a treponemal test [5]. In addition to the traditional screening algorithm for syphilis, the reverse algorithm is recommended [7-9]. The first step in the reverse algorithm begins with a treponemal test, followed by a nontreponemal test if the treponemal test results are reactive. In cases where both treponemal and nontreponemal test results are reactive using the reverse algorithm, performing a second, different treponemal test is recommended [9]. The reverse algorithm is capable of detecting both past and active infections. The European Center for Disease Prevention and Control (ECDC) has suggested another algorithm in which a second and different treponemal test follows a reactive treponemal screening test. Nontreponemal tests are not recommended in this algorithm [6].

We used RPR, TPHA, and CLIA tests in our study. Rapid plasma reagin, a nontreponemal test, is preferred in the laboratory diagnosis of syphilis and treatment follow-up due to its ease of application and low cost. Among the treponemal tests, TPHA tests are used for screening and confirmation purposes [1]. In this study, we aimed to compare the diagnostic performance of reverse, traditional, and ECDC algorithms according to the clinical diagnosis of syphilis using RPR, CLIA, and TPHA tests.

MATERIALS AND METHODS

From March 2023 to July 2023, a total of 297 patients from various units of our hospital, suspected of having syphilis, were included in the study. The serum samples of each patient were stored at -20°C until the analysis. All samples were analyzed using RPR, CLIA, and TPHA tests, and each patient sample was examined separately with three different algorithms. A total of 105 patients have been diagnosed with syphilis.

In the traditional algorithm, it began with RPR, a nontreponemal test; if reactive, it was confirmed with treponemal tests (TPHA, CLIA). In the reverse algorithm, the treponemal test (CLIA) served as the screening test, and after reactive results, the nontreponemal test was continued. If the nontreponemal test resulted in nonreactive, the TPHA test was applied. In the ECDC algorithm, screening was performed with CLIA, a treponemal test. If the test result was reactive, a different treponemal test, TPHA, was studied as a reflex test (Figure 1).

Clinical diagnosis of syphilis

According to the guidelines, syphilis was clinically diagnosed using personal history (including clinical characteristics and the patient's sexual history) along with serological tests. Syphilis is categorized into stages: primary (ulcer-chancre, usually accompanied by regional lymphadenopathy), secondary (skin rash, mucocutaneous lesions, and lymphadenopathy), early-late latent (asymptomatic, with a possible history of infection supported by a reactive serological test and normal cerebrospinal fluid), and tertiary (syphilis acquired more than one year prior, presenting with cardiac or gummatous lesions) [1]. Clinical diagnosis is regarded as the gold standard.

Serological tests

A qualitative RPR test (SPINREACT, Citra Santa Coloma, SPAIN) was used as a nontreponemal test. Blood samples were centrifuged at 2,000g for 10 minutes. According to manufacturers recommendations, 20 µL of RPR carbon was added to 50 µL of the sample, brought to room temperature, mixed on the slide in a mechanical rotator for 8 minutes, and evaluated under good light. In the qualitative method, positive evaluations were given to clusters, and negative evaluations to no clustering.

Two treponemal tests were used: CLIA and TPHA. For the first treponemal test, serum samples were tested using the VIRCLIA® (Syphilis® IgG+IgM MONOTEST, Vircell, Spain) test and the results were evalu-

ated using a special software program. In line with the manufacturers recommendations, results with ≥ 1.1 COI (cut-off index) units were considered as positive. As the second treponemal test, serum samples were studied with the TPHA test (Rapid Labs, Colchester, UK). According to the manufacturer's recommendations, the TPHA test was performed by diluting the sera (at 1:80, 1:160 and 1:240 ratios) and then incubating them separately with the test and control cell suspensions in U-bottom microplate wells, followed by examination for hemagglutination. Observation of agglutination at 1:80 dilution in the patient serum was considered positive.

Statistical analysis

The patient test results and demographic data were obtained from the hospital information system. Statistical Packages for the Social Sciences (SPSS), software version 22.0 (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA) was used for statistical data analysis. Qualitative results were given as positive/negative according to the tests and algorithms and the gender of the patients were recorded as categorical variables, while the quantitative results were given as COI obtained by the CLIA test and the ages of the patients were recorded as continuous variables. Numerical data are presented as numbers (n), percentages (%) and analyzed as mean (± standard deviation). The chi-squared test was used to compare categorical variables, and the Mann-Whitney U test was used to compare mean values. The agreement between qualitative results was analyzed by calculating Cohen's kappa value and percentage agreement. According to the kappa value, the agreement was classified as poor (≤ 0.20), low (0.21 - 0.40), moderate (0.41 - 0.60), good (0.61 - 0.80) and very good level (0.81 - 1.00). Considering clinical diagnosis as the gold standard, the sensitivity, specificity, PPV and NPV of the traditional, reverse, and ECDC algorithms were calculated. Receiver operating characteristic (ROC) analysis was conducted by accepting clinical diagnosis as the gold standard, determining the CLIA COI value, which has high sensitivity and specificity and can be used to predict syphilis diagnosis serologically. In all statistical analyses, a p-value of < 0.05 was considered statistically significant.

RESULTS

There were 297 patients suspected of having syphilis, 105 were clinically diagnosed with syphilis (35.3%). The clinical information for patients with syphilis (n: 105) is listed in Table 1. The mean age of 297 patients were calculated as 37.6 ± 13.9 years. The study group consisted of 54.5% (n: 162) male and 45.5% (n: 135) female patients. The mean age of patients diagnosed with syphilis was calculated as 39.4 ± 13.7 years which were found to be older than that of the patients with a negative syphilis diagnosis (36.7 ± 14.1 years) ($p = 0.045$). Male patients (88.6%, n: 93) and HIV positive patients (66.7%, n: 70) were statistically more prevalent among those clinically diagnosed with syphilis. In the traditional algorithm the first serological test was the RPR test. Second and third step serological tests, which were CLIA and TPHA, respectively, were used to confirmed the results. According to the traditional algorithm there were 44 (14.8%) serologically positive patients and there were no false positive results (Figure 1 and Table 2).

In the reverse and ECDC algorithms, the first step of the serological test was the CLIA test. According to the CLIA test, 108 (36.4%) samples were found to be positive. In the reverse algorithm, the second step of the serological test was the RPR test, which identified 44 patients as positive and 64 as negative. The third step serological test in the reverse algorithm was the TPHA test. With this test, of the 108 patients assessed, 3 were found to be negative and 105 were found to be positive, consistent with the clinical diagnosis. In the ECDC algorithm, the second step serological test was the TPHA test, which confirmed that 105 of the 108 CLIA positive patients were also positive on the TPHA test. The serological test results according to three different algorithms are shown in Figure 1 and Table 2.

As a result, 14.8% (44/297) of the samples were evaluated as positive for syphilis using the traditional algorithm, while 35.3% (105/297) were positive with the ECDC and reverse algorithms. Using clinical diagnosis as a reference, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the traditional algorithm were found to be 41.9%, 100%, 100%, and 75.9%, respectively. For the reverse and ECDC algorithms, sensitivities, specificities, PPV, and NPV were 100% across all parameters (Table 3).

Although the sensitivity, specificity, PPV, and NPV values of the reverse and ECDC algorithms were the same and consistent with the clinical diagnosis, differences were found between the results of these two treponemal tests (CLIA and TPHA).

When the sensitivity, specificity, PPV, NPV values were examined separately on the basis of the tests, these values were, respectively, 97.2%, 100%, 100%, 98.4% for the CLIA test, 41.9%, 100%, 100%, 75.9% for the RPR test, and 100% for all parameters for the TPHA test.

Syphilis cases (n: 105) were classified into various stages of syphilis to evaluate the three serological algorithms. The traditional syphilis testing algorithm demonstrated low sensitivity for primary syphilis (0.9%) and early/late latent syphilis (66.7%). In comparison, both the reverse and ECDC algorithms exhibited high sensitivity at different stages of syphilis ($p < 0.001$) (Table 3).

Among the patients whose diagnosis was missed by the traditional algorithm (61/105) according to the RPR negativity, (47/61) 77% of them were composed of treated and 23% (14/61) of them were composed of untreated patients. One patient was diagnosed with prima-

Table 1. Clinical data from syphilis patients.

Characteristic	n = 105
Mean age (years)	39.4 (SD: ± 13.7)
Male, mean age (years)	39.3 (SD: ± 13.5)
Female, mean age (years)	40.3 (SD: ± 15.9)
Gender	
Male	93 (88.6%)
Female	12 (11.4%)
Race/ethnicity	
Mediterian	102 (97.1%)
Other	3 (2.9%)
Pregnancy status (n = 8)	
Pregnant	1 (12.5%)
Not pregnant	7 (87.5%)
HIV status	
Positive	70 (66.7%)
Negative	35 (33.3%)
Prior history of syphilis	
Yes	42 (40.0%)
No	63 (60.0%)
Clinical phase	
Primary	1 (0.9%)
Secondary	13 (12.4%)
Tertiary	21 (20.0%)
Early latent	7 (6.7%)
Late latent	63 (60.0%)
Treatment status	
Untreated	14 (13.3%)
Treated	91 (86.7%)

HIV - human immunodeficiency virus, STD - sexually transmitted disease, SD - standard deviation.

Table 2. Performance of three syphilis algorithms in syphilis serodiagnosis.

Algorithms		Clinical and serological diagnosis of syphilis		Sensitivity	Specificity	PPV	NPV
		positive	negative				
Traditional	positive	44	0	41.9	100	100	75.9
	negative	61	192				
Reverse	positive	105	0	100	100	100	100
	negative	0	192				
ECDC	positive	105	0	100	100	100	100
	negative	0	192				

PPV - positive predictive value, NPV - negative predictive value, ECDC - European Center for Disease Prevention and Control.

Table 3. Evaluation of the seropositivity with three algorithms at different stages of syphilis.

Clinical diagnosis n (%)		Seropositivity		
		Traditional algorithm	Reverse algorithm	ECDC algorithm
Primary	1 (0.9%)	-	1	1
Secondary	13 (12.4%)	13	13	13
Tertiary	21 (20.0%)	21	21	21
Early latent	7 (6.7%)	-	7	7
Late latent	63 (60.0%)	-	63	63

ECDC - European Centre for Disease Prevention and Control.

Table 4. Characteristics of 61 cases of missed diagnoses with the traditional algorithm.

Treatment history	Primary Cases	Secondary Cases	Early Latent Cases	Late Latent Cases	Tertiary Cases	Total n (%)
Treated	-	-	3	44	-	47 (77.0)
Untreated	1	-	3	10	-	14 (23.0)
Total n (%)	1 (1.6)	-	6 (9.9)	54 (88.5)	-	61 (100.0)

ry syphilis, while sixty had a diagnosis of latent or post-treatment syphilis (Table 4).

As a first-line serological test, RPR was reactive in 44 patients in the traditional algorithm, while CLIA was found reactive in 108 patients in the other two algorithms. The traditional and reverse algorithms were found to have moderate agreement (kappa value 0.483, $p < 0.001$). Very good agreement (kappa value 1.0, $p < 0.001$) was found between ECDC and the reverse algorithm.

To predict serological diagnosis, CLIA COI values with the highest sensitivity and specificity were examined using receiver operating characteristic (ROC) analysis. In our study, clinical diagnosis was accepted as the gold standard; the most appropriate CLIA COI value is 0.986, with 100% sensitivity and 98.4% specificity. According to ROC analysis, when the CLIA COI value was accepted as 1.229, both sensitivity and specificity were determined to be 99.0%. The area under the ROC (AUC) was calculated as 0.999 (Figure 2).

DISCUSSION

Serological tests are prediagnostic tests that are widely used for screening and treatment follow-up of syphilis. Serological tests are divided into two groups: treponemal and nontreponemal. Treponemal tests become reactive a few weeks after infection and remain reactive throughout life, even after successful treatment. Nontreponemal tests are used to evaluate the activity of the disease and response to treatment. Moreover, reaginic antibody may be negative in cases of late latent or post-treatment syphilis (due to seroreversion). Serological tests may be false-positive or false-negative at different stages of the disease and may be inadequate in evaluating the response to treatment, depending on the chosen method. For this reason, tests are used in combination, and algorithms are created for disease screening, diagnosis, and follow-up [1,2].

The guidelines indicate that serological tests have limitations in diagnosing syphilis and recommend that the diagnosis be supported by the patient's clinical findings (patient history, symptoms and signs) [3]. In the current study, three algorithms were evaluated using clinical diagnoses, TPHA, RPR, and CLIA test results.

Tong et al. evaluated the algorithms in a population (n: 2,749) undergoing syphilis testing for screening, for diagnosis, or for monitoring response to treatment. In their study, which regarded clinical diagnosis as the gold standard, they reported a sensitivity of 75.81% using the traditional algorithm. They found the sensitivity in the reverse and ECDC algorithms to be 99.38% and 99.85%, respectively [10]. In our study, we found that the traditional algorithm had a low sensitivity of 41.9%, consistent with some studies, and 44 of 105 patients were diagnosed with syphilis [11-15]. Since the first step in the traditional algorithm is a nontreponemal test, only 44 patients were referred to the second step, the treponemal test. So in the traditional algorithm, syphilis patients missed by the RPR test are not studied with the TPHA test. Also, the sensitivity of the reverse

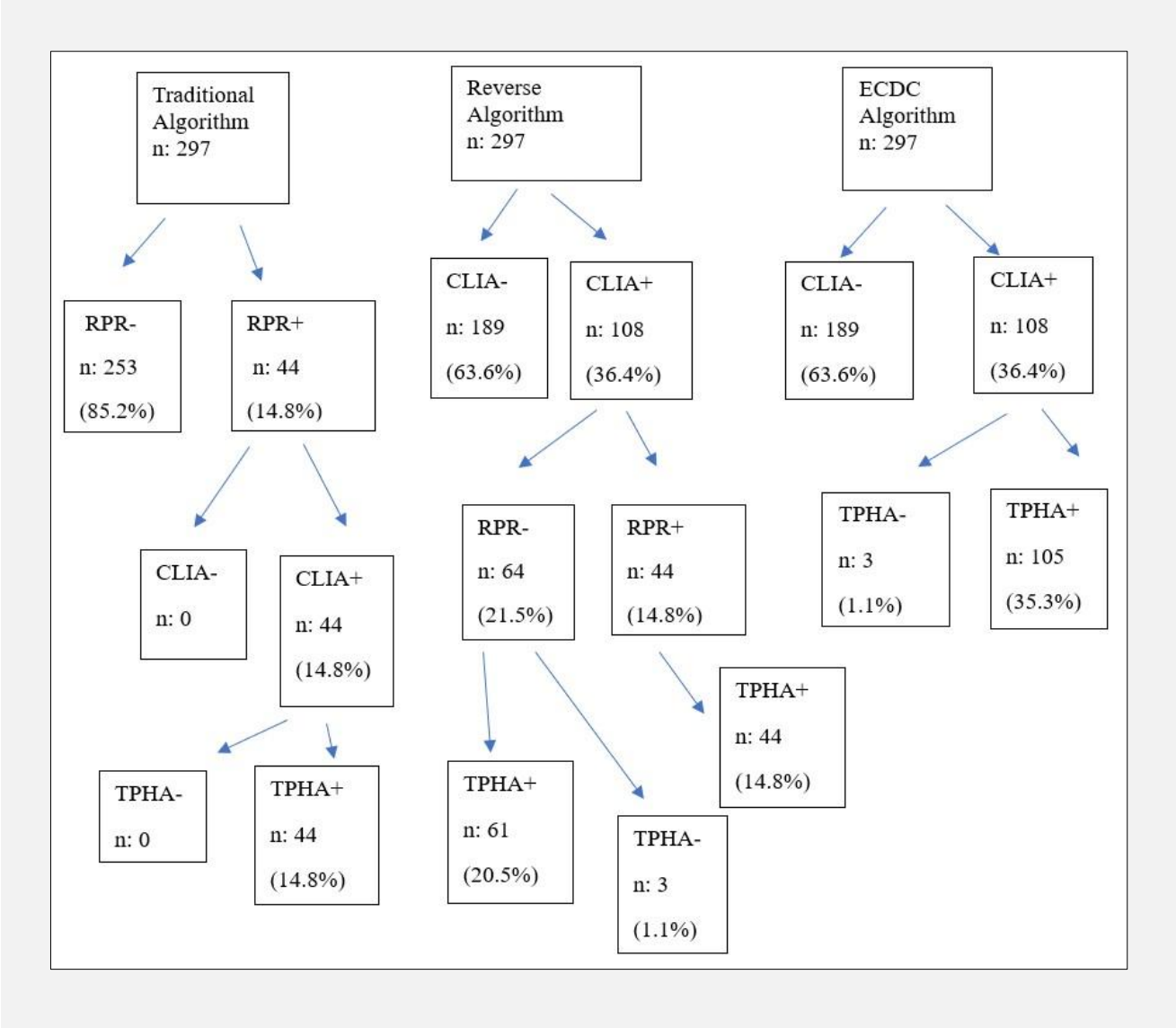

Figure 1. Serological test results based on conventional, reverse, and ECDC algorithms.

ECDC - European Centre for Disease Prevention and Control, RPR - rapid plasma regain, CLIA - chemiluminescence immunoassay, TPHA - *Treponema pallidum* hemagglutination.

and ECDC algorithms in our study was the same as Tong's results.

The overall prevalence of syphilis in our hospital for the year 2023 was 16.6% (654 out of 3,937 patients). But in our study group, 35.3% (105 out of 297) patients were diagnosed with syphilis by the clinicians. The lower sensitivity of the traditional algorithm and RPR test in our study compared to Tong et al. might be due to differences in the study groups. Tong et al. conducted their studies in a population with a seroprevalence of 11.40%. In contrast, our study group exhibited a higher prevalence of 35.3% because we focused exclusively on patients suspected of having syphilis, excluding those who came to the hospital for routine screening. Additionally, most patients in our study group had latent syphilis, which decreased the sensitivity of the RPR test. Previous studies have indicated that the presence of reaginic antibodies can lead to false-negative results in the RPR test following treatment [1].

In our study 61 patients were excluded from positive serodiagnosis because of a missed diagnosis rate of 58.1% in the RPR test (61 of 105 subjects). One patient was diagnosed with primary syphilis, while sixty had a diagnosis of latent or post-treatment syphilis. One case of primary syphilis and thirteen cases of latent syphilis were not treated. Among the 61 patients missed by the

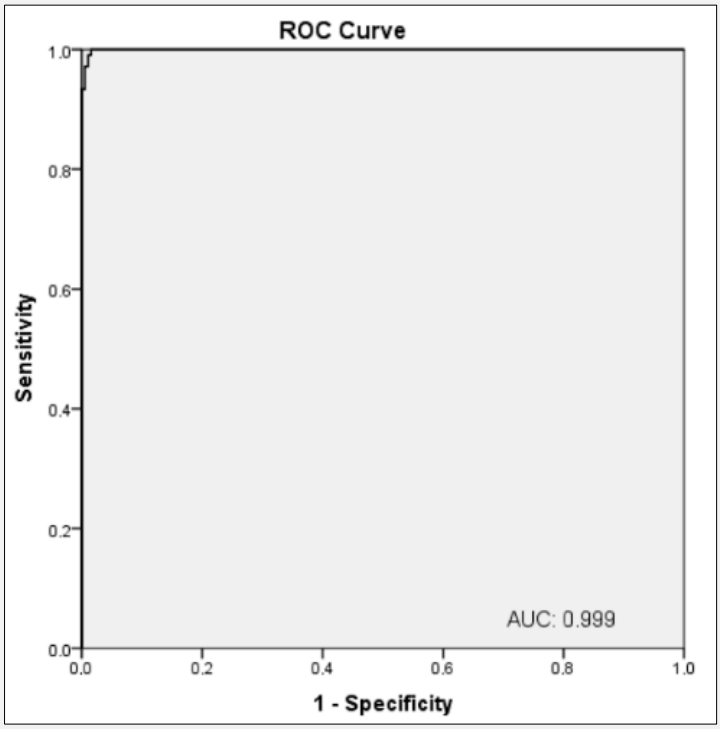

Figure 2. ROC analysis performed with CLIA COI values, accepting clinical diagnosis as the gold standard.

CLIA COI - chemiluminescence immunoassay cut-off index, ROC - receiver operating characteristic, AUC - area under the curve.

RPR test, 60 had latent syphilis, and 47 of these had received treatment. Therefore, attention should be directed to missed diagnoses resulting from the traditional syphilis testing algorithm [10]. It seems that the difference between the diagnostic performances of traditional and reverse algorithms can be explained by the fact that the traditional algorithm can detect only active infection [1,2].

Tong et al. concluded that, except for biological false-positive reactions, if the RPR test was positive, the TPHA test would certainly be positive. However, the converse was not necessarily true [10]. In this study, 61 RPR negative patients among 105 clinically diagnosed individuals tested positive for TPHA results. Additionally, these patients had reactive CLIA tests along with their clinical diagnoses. The limited number of suspicious patients evaluated in our study may explain the absence of false positives in the RPR results.

As a first-line serological test, RPR was reactive in 44 patients in the traditional algorithm, while CLIA was found reactive in 108 patients in the other two algorithms. The traditional and reverse algorithms found moderate agreement (kappa value 0.483, $p < 0.001$). Very good agreement (kappa value 1.0 and $p < 0.001$) was found between ECDC and the reverse algorithm. In the study conducted by Nah et al., they investigated the results of individuals who came for routine health check-ups, and they found low agreement (kappa value 0.191) between the traditional and reverse algorithms [15]. Chen et al. compared traditional and ECDC algorithms with the reverse algorithm in HIV-positive syphilis patients. The kappa value was reported to be in good agreement (0.668) in HIV-infected individuals with both algorithms. They also found the reverse algorithm to be highly sensitive. Furthermore, they reported that the traditional algorithm had a misdiagnosis rate of 42% [16]. Differences in study groups can influence the results of algorithm compatibility. Therefore, when selecting an algorithm, it is essential to consider both the group being studied and the patient population. Additionally, properly choosing the first step test in the algorithms is crucial to avoid false positives and false negatives.

When the sensitivity, specificity, PPV, NPV values were examined separately on the basis of the tests, these values were, respectively, 97.2%, 100%, 100%, 98.4% for the CLIA test, 41.9%, 100%, 100%, 75.9% for the RPR test, and 100%, 100%, 100%, 100% for the TPHA

test. Similar studies have reported varying sensitivity results, with treponemal tests demonstrating higher sensitivity levels [15,17,18].

In our study, although the algorithm results indicated 100% sensitivity (ECDC and reverse), we found three false positives when evaluated on a test basis using the first-step test, CLIA. Some studies that directly compared the reverse and traditional algorithms reported false-positive rates when using the reverse algorithm for screening [11,18]. In the study conducted by Lee et al., based on the TPPA test, they evaluated the test sensitivities. It was stated that the ECLIA test gave results with high sensitivity and specificity and that the COI value determined by ROC analysis would be helpful in predicting the TPPA test to optimize the sensitivities and specificities [17]. To predict serological diagnosis, CLIA COI values with the highest sensitivity and specificity were examined using receiver operating characteristic (ROC) analysis. In our study, clinical diagnosis was accepted as the gold standard; the most appropriate CLIA COI value is 0.986, with 100% sensitivity and 98.4% specificity. According to ROC analysis, when the CLIA COI value was accepted as 1.229, both sensitivity and specificity were determined to be 99.0% (Figure 2).

It can be said that the first step of the screening tests primarily determines the diagnostic performance of the algorithm. Additionally, using automated systems in the first step especially offers advantages such as providing standard results for many samples and avoiding time consumption. In the study by Park et al., Elecsys Syphilis, the first screening test of the reverse and ECDC algorithms, was compared with five other automated treponemal tests. Its sensitivity and specificity were found to be 99.4% and 100%, respectively, demonstrating the best diagnostic accuracy [18]. Large-volume laboratories, especially, may be advised to use highly sensitive, user-friendly and cost-effective automatic systems in the first step of the algorithms [19,20]. In this study, we selected the CLIA automated test as the initial step in the reverse algorithm. We believe it would benefit serological diagnosis if each center determined its own COIs by conducting ROC analyses using high-sensitivity automated systems along with the gold standard methods selected for their specific patient groups. Apart from the tests selected in the studies, the characteristics of the subjects and the distribution of syphilis stages may also affect the compatibility between the algorithms. Our study found a very good agreement between the ECDC and reverse algorithms (kappa value 1.0 and $p < 0.001$). Both the reverse and the ECDC algorithms showed higher seropositivity rates compared to the traditional algorithm, particularly in cases of latent syphilis. This result suggests that omitting the nontreponemal test in the reverse algorithm and utilizing a second treponemal test alone as a confirmatory test would be sufficient. The *Treponema pallidum* hemagglutination test is generally recommended as a confirmatory test due to its superior performance among agglutination tests and its higher sensitivity and specificity [21].

This study has some limitations. First, our study group primarily consisted of patients who were suspected of having syphilis and at different stages of the disease. Our findings may not be generalizable to populations with lower syphilis prevalence. Nonetheless, the study represents the population of a tertiary hospital with a low sample size in an urban area. In summary, our study demonstrates that treponemal antibody tests are superior when employed as the initial step in diagnosing syphilis in patients with suspected syphilis cases. In diagnosing suspected syphilis cases, the reverse algorithm and ECDC algorithms that use treponemal tests as the first step were found to be superior to the traditional algorithm.

However, laboratories should select the most suitable algorithm by considering seroprevalence, cost, ease of use, suitability for automation, and patient demographics. Nontreponemal tests should be used solely to evaluate disease activity and response to therapy. As a result, choosing the optimal algorithm for suspected syphilis cases and patients with latent syphilis is crucial for diagnosis, treatment initiation, and treatment follow-up. Our study provides the first data from our institution on the diagnosis of syphilis. We believe this research will enrich the literature regarding the routine utilization of syphilis diagnostic algorithms in medical microbiology laboratories by highlighting the significance of standardizing syphilis tests and developing an optimal management approach for syphilis.

Informed Consent Statement:

The study was conducted with the permission of the Ethical Committee of Training and Research Hospital (Date: 13.04.2023, Decision No.: 2023-0795/19). All methods were performed in accordance with the relevant guidelines and regulations.

Informed consent was obtained from all subjects and/or their legal guardians.

Authors confirm that the consent form for participation in this study was distributed to all participants and that they signed it.

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Declaration of Interest:

The authors declare no conflicts of interest.

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