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Research Article

Evaluation of syphilis screening results in donors applying to a transfusion center of a tertiary hospital

Üçüncü Basamak Bir Hastanenin Transfüzyon Merkezine Başvuran Donörlerde Sifiliz Tarama Sonuçlarının Değerlendirilmesi

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Abstract

Aim: In blood banking, the significance of diagnosing syphilis, a condition caused by Treponema pallidum, cannot be overstated. It necessitates the adoption of the most appropriate algorithm for catching possible cases among donors, thereby minimizing donor loss. The World Health Organization in 2003, and the European Centre for Disease Prevention and Control in 2010, advised starting syphilis screenings with Treponemal tests. This study aimed to investigate the outcomes of confirmatory tests conducted on blood donor candidates with reactive Enzyme-Linked Immunosorbent Assay (ELISA) test results in syphilis screening.

Material and Methods: In this retrospective study, 69,127 donors who applied as blood donors to the blood bank of Ankara Gülhane Training and Research Hospital between 2014 and 2021 were examined. Specimens from donor candidates who tested reactive in the syphilis screening test were dispatched to the Microbiology Reference Laboratory of the Turkey Public Health Institution for verification tests. The Fluorescent Treponemal Antibody Absorption (FTA-ABS) or Treponema Pallidum Hemagglutination Assay (TPHA) tests were utilized as the verification tests.

Results: Reactive test results were obtained repeatedly in 128 donors (0.18%). As a confirmatory test, TPHA was administered to 32 donors, resulting in 11 positive outcomes (34.3%) (False positivity ratio = 65.7%). FTA-ABS was performed as a verification test on 96 donors, with 59 (61.4%) testing positive (False positivity ratio = 38.6%). Out of 48 donors with an ELISA signal-to-cutoff ratio above five, the FTA-ABS test was conducted on 42, yielding 41 positive and one negative result.

Conclusion: The transmission of Treponema pallidum through blood transfusion is a significant adverse event, so the most suitable tests should be used for the screening of blood donors. This study suggests that using FTA-ABS as a confirmatory test for ELISA-reactive donors improves syphilis detection accuracy.

Keywords: Blood donor screening; confirmatory tests; syphilis; Treponema pallidum

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ÖZ

Amaç: Kan bankacılığında Treponema pallidum'un neden olduğu sifiliz tanısı halk sağlığı açısından önemlidir. Donörler arasındaki olası vakaların yakalanması ve böylece donör kaybının en aza indirilmesi için en uygun algoritmanın benimsenmesi gerekmektedir. 2003 yılında Dünya Sağlık Örgütü ve 2010 yılında Avrupa Hastalık Önleme ve Kontrol Merkezi, sifiliz taramalarına Treponemal testlerle başlanmasını tavsiye etti. Bu çalışmada, kan bağışçısı adaylarında sifiliz taramasında reaktif Enzime Bağlı İmmünosorbent Test (ELISA) sonuçları ile yapılan doğrulayıcı testlerin sonuçlarının araştırılması amaçlandı.

Gereç ve Yöntemler: Retrospektif olarak yapılan bu çalışmada, 2014-2021 yılları arasında Ankara Gülhane Eğitim ve Araştırma Hastanesinin kan bankasına kan bağışçısı olarak başvuran 69.127 bağışçı incelendi. Sifiliz tarama testinde reaktif çıkan donör adaylarından alınan örnekler, doğrulama testleri için Türkiye Halk Sağlığı Kurumu Mikrobiyoloji Referans Laboratuvarı'na gönderildi. Doğrulama testleri olarak Floresan Treponemal Antikor Emilimi (FTA-ABS) veya Treponema Pallidum Hemaglütinasyon Testi (TPHA) testleri kullanıldı.

Bulgular: 128 donörde (%0,18) tekrar tekrar reaktif test sonuçları elde edildi. Doğrulayıcı bir test olarak 32 donöre TPHA uygulandı ve 11 pozitif sonuç (%34,3) elde edildi (Yanlış pozitiflik oranı = %65,7). FTA-ABS, doğrulama testi olarak 96 donörde yapıldı ve 59'unun (%61,4) testi pozitif çıktı (Yanlış pozitiflik oranı = %38,6). ELISA sinyal-kesme oranı beşin üzerinde olan 48 donörden 42'sinde FTA-ABS testi yapıldı ve 41 pozitif ve bir negatif sonuç elde edildi.

Sonuçlar: Kan transfüzyonu ile ilişkili Treponema pallidum bulaşması önemli bir istenmeyen olay olduğundan, kan donörlerinin taranması için en uygun testlerin kullanılması gerekmektedir. Bu çalışma, FTA-ABS'nin ELISA-reaktif donörler için doğrulayıcı bir test olarak kullanılmasının, sifiliz tespit doğrulanmasını arttırdığını göstermektedir.

Anahtar Kelimeler: Kan donör taraması; doğrulama testleri; sifiliz; Treponema pallidum

Introduction

Syphilis remains a significant public health issue worldwide. The disease is caused by Treponema pallidum (T. pallidum), a spirochete bacterium, transmitted either sexually or from mother to infant [1]. According to data from the Centers for Disease Control and Prevention (CDC), there were 133,495 new cases of syphilis reported in the United States in 2020. The number of patients in the primary and secondary stages, which are highly infectious, rose by 6.8% in 2020 compared to the figures from the 2000s [2]. In our country, there were a total of 3,533 reported cases in 2022, marking an increase of approximately 7.7 times compared to the numbers from 2010 [3].

Serologic tests for diagnosing syphilis fall into two categories: treponemal and non-treponemal tests. These serologic tests are currently the most effective tools for screening and diagnosing syphilis; they can indicate the disease's stage, monitor treatment response, and may be the sole evidence of disease in cases of latent infection [4]. Non-treponemal tests detect immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies produced against lipid antigens, such as cardiolipin and lecithins, that are released due to cell damage from both the host and the bacterium. These antibodies are typically detectable from the sixth week of infection [5]. The tests, which can provide quantitative results, include the Rapid Plasma Reagin (RPR) and the Venereal Disease Research Laboratory (VDRL) tests. A fourfold decrease in titers in these tests is interpreted as a successful treatment response [6].

The ability to detect antibodies against T. pallidum antigens using automated methods such as the Enzyme Immunoassay (EIA) and the Chemiluminescence Immunoassay (CLIA) has highlighted the importance of treponemal tests as a primary screening tool. Consequently, the World Health Organization (WHO) in 2003 and the European Center for Disease Prevention and Control (ECDC) in 2010 recommended initiating syphilis screening with treponemal tests [7, 8]. There are three different diagnostic algorithms for syphilis: the classical algorithm, the reverse algorithm, and the ECDC algorithm, each selected based on the tests used in screening and confirmation. Since each algorithm has its own set of advantages and disadvantages, there is no definitive guidance on which one should be universally applied. Therefore, this study aimed to investigate the outcomes of confirmatory tests conducted on blood donor candidates with reactive ELISA test results in syphilis screening.

Material and Methods

This retrospective study was conducted on patients who admitted to the Blood Center of the Ankara Gülhane Training and Research Hospital, between January 2014 and December 2021. The study was approved by the Ankara Gülhane Training and Research Hospital Ethics Committee (Date: 16.05.2023, Decision No: 2023-213) and was carried out in accordance with the relevant ethical guidelines and the Helsinki Declaration (2013 Brazil revision). Due to the retrospective design of the study, the local ethics committee waived the necessity for informed consent.

In this study, 69,127 donors under the age of 18 who admitted to the Blood Center of the hospital during the aforementioned years were retrospectively evaluated. The Architect i2000SR EIA test was used as a routine screening test for HIV Ag/Ab complex, anti-HCV, syphilis ELISA, HBsAg, and anti-HBc in serum samples from all individuals applying to the blood bank as donors. A concentration of ≥ 1 mIU/ml in serum samples was considered reactive for the syphilis antibody.

According to the National Guidelines for the Preparation, Use, and Quality Assurance of Blood and Blood Components, donors with reactive results from syphilis screening tests were classified under "recurrent reactivity" if any of the repeated tests remained reactive after two additional tests using the same method. According to the definition in the same guideline, results that corresponded to 10% of the threshold were considered 'indeterminate', and the specimen's screening test result was recorded as 'reactive'. Donor samples that exhibited recurrent reactive results were forwarded to the Microbiology Reference Laboratory of the Public Health Agency of Turkey for confirmatory testing. Confirmatory tests were conducted using either FTA-ABS IgG/IgM (Euroimmun, Germany) or TPHA (Plasmatec, UK).

Statistical analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean ± standard deviation while non-normally distributed variables are given as median (min – max). Categorical variables are given as numbers and percentages.

Results

Between 2014 and 2021, all 69,127 donors screened for syphilis using ELISA were first-time donors, and 0.18% of them (n=128) had recurrent reactive test results. The annual numbers of positive syphilis screening tests, as part of the conducted microbiological screening tests, are shown in Figure 1. The mean age of these donors was 41.8±8.6 years, and the vast majority were male (93.7%, n=120). Additionally, the majority of the donors were married (89.8%) and had an education level of high school or below (64.8%) (Table 1).

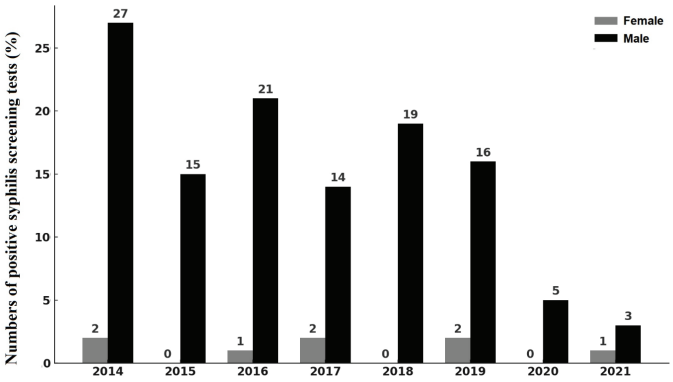

Figure 1. The annual numbers of positive syphilis screening tests.

Table 1. Demographic and clinical characteristics of donors who admitted to the blood center of the hospital.

Variables	All population n = 128
Age, years	41.8 ± 8.6
Gender, n (%)	
Female	8 (6.3)
Male	120 (93.7)
Marital status, n (%)	
Married	115 (89.8)
Not married	13 (10.2)
Education level, n (%)	
≤High school	83 (64.8)
>High school	45 (35.2)
FTA-ABS, n (%)	n = 96
Positivity	59 (61.4)
Negative	37 (38.6)
TPHA, n (%)	n = 32
Positivity	11 (34.3)
Negative	21 (65.7)

Numerical variables were shown as mean ± standard deviation. Categorical variables were shown as numbers (%). FTA-ABS, Fluorescent Treponemal Antibody Absorption; TPHA, Treponema Pallidum Hemagglutination Assay.

TPHA was conducted as a confirmatory test on 32 donors, with 11 donors (34.3%) yielding positive results. The ELISA test result for 65.7% of the donors who underwent TPHA as a confirmatory test was assessed as false positive. Additionally, FTA-ABS was administered as a confirmatory test to 96 donors, of which 59 donors (61.4%) received positive results. The ELISA test result for 38.6% of the donors who underwent FTA-ABS as a confirmatory test was considered false positive.

The FTA-ABS IgM result was negative in all 37 donors with a negative FTA-ABS IgG. Among the 58 donors with a positive FTA-ABS IgG, the FTA-ABS IgM result was positive in 5 donors. Additionally, the FTA-ABS IgM result was positive in 1 donor whose FTA-ABS IgG was at the limit value (Table 2).

Table 2. Summary of FTA-ABS test results

FTA-ABS IgM	FTA-ABS IgG		
	Negative n = 37	Positive n = 58	At the Limit n = 1
Negative, n (%)	37 (100)	53 (91.4)	0
Positive, n (%)	0	5 (8.6)	1 (100)

Categorical variables were shown as numbers (%). FTA-ABS, Fluorescent Treponemal Antibody Absorption; TPHA, Treponema Pallidum Hemagglutination Assay.

Among the donors, 10 had screening test results classified as "indeterminate" according to the national guideline. For confirmatory testing, 5 of these donors were tested with FTA-ABS and the remaining 5 with TPHA. Among the 5 donors who underwent FTA-ABS, 3 tested positive and 2 tested negative. Of the 5 donors tested with TPHA, 2 were positive and 3 were negative.

There were 48 donors with an ELISA signal-to-cutoff value above 5. Of these, 42 were tested with FTA-ABS, resulting in 41 positive and 1 negative outcome. Among the same group of 48 donors, 6 were tested for TPHA, with 5 testing positive and 1 testing negative.

Discussion

In the traditional approach to syphilis diagnosis, a non-treponemal test is initially employed for screening purposes. This method, however, is susceptible to a range of factors that can lead to false-positive results. Such factors include the presence of other infections (for instance, HIV), autoimmune disorders, recent vaccinations, intravenous drug use, pregnancy, and older age [9]. Despite these challenges, the classical algorithm dictates that a positive result from a non-treponemal test should be followed up with a treponemal test for confirmation. A diagnosis of syphilis is considered when both tests return positive results. Over time, the prevalence of the classical algorithm's use has waned. This decline can be attributed to several reasons: non-treponemal tests demand interpretative expertise that is not universally available, the process is time-consuming, which limits its utility in rapid screening scenarios [10]. Moreover, the sensitivity of non-treponemal tests may diminish in patients at the very early or late stages of syphilis, thereby reducing their effectiveness in accurately diagnosing the disease [11]. These limitations underscore the need for alternative diagnostic strategies that can overcome the shortcomings of the classical algorithm.

The reverse algorithm, increasingly adopted in recent years, inverts the traditional approach to syphilis screening. This methodology initiates with a treponemal test to screen for syphilis. Upon obtaining a positive result, a non-treponemal test is then conducted to confirm the diagnosis. The integration of treponemal tests into automated systems has significantly streamlined the screening process, particularly in facilities handling large volumes of samples, such as blood banks. In 2011, the CDC reported the reverse algorithm as a complementary method to the classical algorithm for diagnosing syphilis in the United States [12]. The reverse algorithm is a valuable diagnostic tool for detecting both early and latent infections. However, it has some limitations. One major drawback is that treponemal tests, integral to this algorithm, are unable to distinguish between current and past infections. This ambiguity necessitates the administration of an additional treponemal test when results from treponemal and non-treponemal tests do not align [13]. Following a positive outcome on the second treponemal test, healthcare professionals may consider initiating treatment for individuals without a history of prior treatment. Conversely, for those with a documented history of treatment and no a new history of suspicious sexual contact, it is not recommended to proceed with a new course of treatment [14].

The ECDC recommends the use of treponemal tests for both screening and confirmation of syphilis [15]. Follow-up treatment of patients diagnosed with this algorithm is conducted according to non-treponemal tests. In our study, syphilis testing using ELISA was conducted on 69,127 blood donors, and 0.18% of the donors had recurrent reactive test results. Compared to reports from other countries, our result was lower than Ethiopia (1,820 per 100,000) [16], India (1,623.7 per 100,000) [17], China (326.8 per 100,000) [18], and Eritrea China (600 per 100,000) [19], but higher than Brazil (140 per 100,000) [20], USA (54.6 per 100,000) [21], and Israel (47 per 100,000) [22]. The discrepancy among various studies may be attributed to variations in the total sample size, the study period, the seroprevalence of syphilis in the local general population, and the test kits used. We attributed the lower syphilis screening positivity in our center to the fact that sexually transmitted disease prevention methods are well implemented in our country and access to treatment is easy. In a study in which 27,365 blood donors were examined in

Turkey, 32 (0.12%) syphilis screening test positive donors were detected and a similar result was obtained in our center [23].

In the study conducted by Lee et al. [24], which involved samples collected from 4,771 individuals, the seroprevalence according to the traditional algorithm was 1.1%, while it was 4.2% with other algorithms. It was noted that the lower seroprevalence achieved through the classical algorithm might pose a threat to public health [24]. Peng et al. reported that the sensitivity and specificity of the classical algorithm were low. They found that the reverse algorithm and ECDC algorithms had a 99.99% concordance and suggested that it was more appropriate to use Enzyme Immunoassay or CLIA tests instead of T. Pallidum Particle Agglutination for screening purposes [25]. At our center, syphilis screening for donor candidates applying for blood donation is conducted using the treponemal test with the ELISA method. For the confirmation of patients whose treponemal test results are recurrently reactive, a second treponemal test is performed on serum samples in the Microbiology Reference Laboratory. TPHA or FTA-ABS was used as a confirmatory test. FTA-ABS demonstrates higher sensitivity in the diagnosis of syphilis compared to TPHA and is often the first test to return positive results [26]. In our study, the rate of false positivity in ELISA tests among donors with reactive screening test results was 65.7% when confirmation was performed with TPHA, and 36.4% when confirmation was performed with FTA-ABS. There is no specific standardization for employing TPHA or FTA-ABS as confirmatory tests across different periods. This lack of standardization hinders effective interpretation of the differences in false positive rates observed in donors who underwent confirmation with TPHA and FTA-ABS in our study.

In our study, the positivity rate in the group confirmed with FTA-ABS was higher compared to the group confirmed with TPHA. The selection of confirmatory tests for patients with positive or indeterminate ELISA test results can vary. Among the donors, 10 had indeterminate syphilis screening results; of these, 3 positive donors were confirmed with FTA-ABS and 2 positive donors were confirmed with TPHA. Simultaneously, antibody detection of 1 mIU/mL and above is regarded as a reactive result, yet the positivity rate of the confirmation test varies according to the antibody titer. In the group of 48 donors who exhibited an ELISA signal cut-off value greater than 5, 95.8% received positive results in their confirmatory tests, whereas 4.2% received negative results. While the false positive rate in the group with an ELISA signal cut-off value of 5 and above was low, further research is needed for more accurate and precise results.

This study had some significant limitations. This study utilized a single-center, retrospective design, which may lead to variations in syphilis seroprevalence across different geographic areas. Furthermore, the results of Enzyme Immunoassay and CLIA were compared across various populations.

Conclusions

Our study indicates that while the initial reactive ELISA tests for syphilis in blood donors at our tertiary hospital transfusion center show a relatively low incidence rate (0.18%), the subsequent confirmatory tests reveal significant differences in false positivity rates between TPHA and FTA-ABS. Specifically, TPHA showed a higher false positivity ratio compared to FTA-ABS, suggesting that FTA-ABS may be a more accurate confirmatory test, especially for cases with an ELISA signal-to-cutoff ratio above five. These findings underscore the importance of using more specific verification tests to reduce the number of healthy donors incorrectly excluded from blood donation due to false positive syphilis screening results. Implementing FTA-ABS as a primary confirmatory test could enhance blood safety and donor retention rates, aligning with global health recommendations for syphilis testing in blood banks.

Conflict of Interest/ Funding

The study received no financial support from any individual or organization, and the authors declare no conflict of interest.

Ethics Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Ankara Gülhane Training and Research Hospital Ethics Committee (Date: 16.05.2023, Decision No: 2023-213).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material: The data that support the findings of this study are available on request from the corresponding author, [Y.Ç.].

Authors' contribution

Concept – Y.Ç., Design- Y.Ç., Data collection and/or processing - Y.Ç., Analysis and/or interpretation - Y.Ç., Writing – Y.Ç. All authors read and approved the final version of the manuscript.

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