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Original Research Article

SEROCURE VS SEROFAST IN SYPHILIS: AN ANALYTICAL CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Syphilis, caused by *Treponema pallidum*, continues to be a global public health problem despite the availability of penicillin. Monitoring treatment outcomes is important, particularly the occurrence of the serofast state, which is influenced by host and disease-related factors. This study aimed to estimate the prevalence of serofast states in adequately treated syphilis patients and analyse the factors associated with serological outcomes. **Materials and Methods:** This analytical cross-sectional study was conducted at the sexually transmitted infection (STI) Clinic of a tertiary care centre in South India between June 2021 and May 2023. A total of 55 patients with serologically confirmed syphilis, adequately treated with benzathine penicillin, were enrolled. All patients underwent baseline assessment and follow-up with Rapid Plasma Reagin (RPR) titres at 6 and 12 months. Cases were classified as "serocure" if a four-fold titre decline was achieved, and "serofast" if titres remained stable or showed less than a four-fold reduction. **Result:** Among the 55 patients, 47 (85.4%) achieved serocure and 8 (14.5%) remained serofast. Primary (n=5) and secondary (n = 13) syphilis showed 100% serocure. Early latent syphilis (n=28) had 25 (89.3%) serocure and 3 (10.7%) serofast. Late latent syphilis (n=9) showed 3 (33.3%) serocure and 6 (66.7%) serofast cases ($p < 0.001$). Serofast was higher in people living with HIV/AIDS (PLHA) (5/16, 31.25%) than in non-PLHA (3/39, 8.33%; $p = 0.024$). Age, gender, and marital status did not significantly affect serological outcomes. Baseline RPR titres ranged 1:8–1:128 in early syphilis and 1:2–1:8 in late latent syphilis. **Conclusion:** Serofast state was strongly associated with late latent syphilis and HIV co-infection, whereas early syphilis cases showed favourable serological cure. Stage-specific monitoring and careful follow-up of PLHA are essential. Early diagnosis and timely treatment can improve cure rates.

INTRODUCTION

Syphilis is a chronic systemic infection caused by Treponema pallidum, transmitted primarily through sexual contact and vertically from mother to child. Despite the discovery and continued availability of penicillin, the disease persists as an important public health issue worldwide. The World Health Organization (WHO) estimated 7.[1] million new syphilis cases globally in 2020.1 The burden is particularly high in low- and middle-income countries, especially in sub-Saharan Africa and South Asia.[2] In India, syphilis continues to be one of the most common sexually transmitted infections (STIs), with a prevalence ranging from 10% to 36% across different populations.[3] Worryingly, studies have documented rising trends in congenital and latent syphilis over the past two decades, despite the availability of effective treatment and preventive measures.[1,2]

The natural history of untreated syphilis is characterised by progression through well-defined stages: primary, secondary, latent, and tertiary. Early syphilis, comprising primary and secondary forms, is considered the most infectious, whereas the early latent stage is non-infectious but may carry a risk of severe long-term complications if untreated.[4] Monitoring of treatment response is based on quantitative non-treponemal serological tests, such as the Rapid Plasma Reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests, which are used to demonstrate a serological decline over time.[5] As recommended by the Centers for Disease Control and Prevention (CDC), patients should be followed up at 6, 12, and 24 months after treatment to assess for a ≥4-fold decline in titres.[6] A failure to demonstrate such reduction or persistence of low

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titres defines the serofast state, which remains a challenge in management because it complicates the interpretation of therapeutic success.[7]

Research from different parts of the world has shown variable rates of serofast response, influenced by several host and disease-related factors. In population-based studies from China, the proportion of serofast cases after treatment ranged from 5% to 41% in different cohorts.[8] Serofast states are more common in patients with late, latent disease than in those with early syphilis.[7] Furthermore, higher baseline non-treponemal titres are associated with a greater likelihood of serological cure, whereas lower pretreatment titres predispose patients to serofast outcomes.[5] However, data from India are limited on this topic. Most Indian studies have largely described the prevalence and clinical manifestations of syphilis, with only a few addressing long-term serological follow-up and outcomes after therapy, particularly in the context of HIV co-infection.[9,10]

Identifying the predictors of serofast responses in an Indian setting is important, as unnecessary retreatment can be avoided when persistent low titres are recognised as part of the serofast state rather than as therapeutic failure. Therefore, this study aimed to estimate the prevalence of serofast state in adequately treated syphilis patients and to analyse the factors associated with this outcome.

MATERIALS AND METHODS

Study Design and Setting

This analytical cross-sectional study included 55 patients with syphilis at the Sexually Transmitted Infection (STI) at a tertiary care centre for two years, from June 2021 to May 2023. Approval for the study was obtained from the Institutional Ethics Committee prior to initiation, and all participants provided written informed consent before enrolment.

Inclusion Criteria

The study included adult patients of either sex who were serologically diagnosed with syphilis and confirmed using the Treponema pallidum haemagglutination assay (TPHA). Only patients who had received adequate treatment with intramuscular benzathine penicillin according to the current national guidelines were considered eligible. Enrolled patients were required to have completed initial therapy and be available for follow-up evaluation at six and twelve months after treatment.

Exclusion Criteria

Patients were excluded if they had received incomplete or inadequate treatment, if treatment adherence could not be confirmed, or if follow-up serological data were unavailable. Individuals treated with alternative regimens other than benzathine pencillin were also excluded.

Methods

All eligible patients underwent a detailed clinical assessment at baseline, including demographic profiles, occupational backgrounds, marital statuses, sexual orientations, and relevant clinical histories. A thorough physical examination was performed, with particular attention to the classical signs of syphilis, such as a chancre, mucocutaneous lesions, condyloma lata, and late stages.

Serological evaluation was performed using the RPR test to determine baseline non-treponemal titres, along with the TPHA confirmation. Patients were then followed up periodically, and RPR titres were reassessed at six and twelve months after treatment. Ancillary investigations included chest radiography, electrocardiography, echocardiography, and basic blood work to rule out systemic complications and comorbidities.

Cases were classified as “serocure” if they demonstrated a four fold or greater decline in RPR titre within six months of treatment for early syphilis or within 12 months for late syphilis. A “serofast” state was defined as a less than four fold decline in titres or persistence of low but stable titres despite adequate therapy. HIV status was determined for all participants, and those who tested positive were categorised as people living with HIV/AIDS (PLHA) for subgroup analyses.

Statistical Analysis

All collected data were entered into a secure electronic database and analysed using IBM SPSS Statistics software v21. Categorical variables were expressed as frequencies and percentages, and continuous variables were summarised as means with standard deviations. Associations between serological outcomes and risk factors were examined using crude odds ratios (OR) or 95% confidence intervals (CI). Statistical significance was set at $p < 0.05$.

RESULTS

Of the 55 patients, most cases were aged between 21 and 30 years (n = 38), followed by 31–40 years (n = 10), >40 years (n = 4), and <20 years (n = 2). Males predominated (n = 43, 78.2%) compared to females (n = 12, 21.8%). Regarding occupation, the majority were employed, either unskilled or skilled (n = 44, 80%), while 7 (12.7%) were unemployed or students, and 4 (7.3%) were professionals. Among the types of syphilis, early latent syphilis was the most common (n = 28, 50.9%), followed by secondary (n = 13, 23.6%), late latent (n = 9, 16.4%), and primary syphilis (n = 5, 9.1%) (Table 1).

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Table 1: Distribution of cases by age, gender, and occupation

Category	Subtypes	N (%)
Age Group (years)	<20	2 (3.6%)
	21–30	38 (69%)
	31–40	10 (18.1%)
	>40	4 (7.2%)
Gender	Female	12 (21.8%)
	Male	43 (78.2%)
Occupation	Unemployed and Students	7 (12.7%)
	Employed (Unskilled/Skilled)	44 (80%)
	Employed (Professionals)	4 (7.35%)
Type of syphilis	Primary syphilis	5 (9.15%)
	Secondary syphilis	13 (23.6%)
	Early latent syphilis	28 (50.9%)
	Late latent syphilis	9 (16.4%)

Among homosexuals, 100% were unmarried, with no cases reported among those married and living with a partner or married but not living with a partner. Among heterosexuals, 70% were married and living with their partner, 21% were unmarried, and 9% were married but not living with their partner. Among bisexuals, 46% were unmarried, 46% were married and living with partner, and 8% were married but not living with partner (Table 2).

Table 2: Distribution of cases by sexual orientation and marital status

Sexual orientation	Marital status		
	Married, not living with partner	Married, living with partner	Unmarried
Homosexuals	0%	0%	100%
Heterosexuals	9%	70%	21%
Bisexuals	8%	46%	46%

The most common age group was 21–30 years (n = 38), and the majority were male (n = 43). Early latent syphilis was the most common type (n = 28), followed by secondary (n = 13), late latent (n = 9), and primary syphilis (n = 5). Overall, 14.5% of the patients were serofast. Serofast was significantly associated with HIV positivity (62% vs. 38%; OR = 0.2, 95% CI: 0.03–0.89, p = 0.024) and late latent syphilis (75% vs. 25%; OR = 0.02, 95% CI: 0.003–0.165, p < 0.0001). No significant association was observed with age (OR = 0.3, 95% CI: 0.06–1.42, p = 0.118), marital status (OR = 0.8, 95% CI: 0.18–3.62, p = 0.78), or gender (OR = 0.6, 95% CI: 0.16–5.20, p = 0.924) (Table 3).

Table 3: Comparison of serofast and serocure states across variables

Category	Subtype	Serofast N (%)	Serocure N (%)	Odds ratio (95% Confidence Interval)	P Value
Age (years)	18-30	4 (50%)	36 (77%)	OR=0.3 (0.06–1.42)	0.118
	30-60	4 (50%)	11 (23%)		
Marital status	Unmarried	4 (50%)	26 (55%)	OR=0.8 (0.18–3.62)	0.78
	Married	4 (50%)	21 (45%)		
Gender	Male	6 (75%)	36 (76%)	OR=0.6 (0.16–5.20)	0.924
	Female	2 (25%)	11 (24%)		
HIV status	HIV Negative	3 (38%)	36 (71%)	OR=0.2 (0.03–0.89)	0.024
	HIV Positive	5 (62%)	11 (29%)		
Stage of syphilis	Early Syphilis (Primary/Secondary/Early Latent)	1 (25%)	44 (94%)	OR=0.02 (0.003–0.165)	<0.0001
	Late Latent Syphilis	7 (75%)	3 (6%)		

DISCUSSION

In our study, the majority of patients were male, and the most affected age group was young adults. Early latent syphilis was the most common, followed by secondary, late latent, and primary syphilis. Most patients were employed in unskilled or skilled jobs, whereas a smaller proportion were either unemployed, students, or professionals. Sena et al. reported a similar age distribution (mean 27.1 years, range 18–53), with 61.7% of patients being male, and most having early syphilis: 46.9% secondary, 24.7% primary, and 28.4% early latent.[11] Zhang et al. studied 517 patients, 73.2% of whom were male and 56.9% married, with the majority having early syphilis (401 primary, 116 secondary), and an HIV prevalence of 18.4%.[12] Leeyaphan et al. analysed 179 early syphilis patients (mean age 31.9 years), 97.2% of whom were male, with the majority having secondary syphilis (89%) and 70% being HIV-positive.[13] Overall, syphilis predominantly affected young adult males, mostly presenting with early stage disease, with findings consistent with previous studies regarding age, sex distribution, and HIV co-infection.

Our study showed that all homosexual participants were unmarried. Among heterosexuals, most were married and living with their partners, while a smaller

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proportion were either unmarried or married but not living with their partners. The bisexual participants included a mix of unmarried individuals, those married and living with a partner, and those married but not living with their partner. Zhang et al. reported that 56.9% of participants were married. A total of 161/517 patients reported having sex with men in the past 6 months, indicating a sizable MSM group, but marital status was still common.[12]

Pastuszczak et al. included 50 patients with early syphilis, equally divided into secondary syphilis (50%) and early latent syphilis (50%) groups. The mean age was 32 years, which is comparable to that of our young adult predominance. Males accounted for 80% of the serofast group and 97% of the cured group.[14] Also aligning with the male predominance in our study. Unmarried status was common among homosexuals, most heterosexuals were married, and male predominance was consistent across studies.

In our study, some patients remained serofast, while the majority achieved serocure. Serofast rates were higher among PLHA than among non-PLHA. By disease stage, late latent syphilis showed a much higher serofast rate than early syphilis, and this difference was significant. Age, gender, and marital status did not significantly affect serofast outcomes. Sena et al. reported a 79.4% serocure rate at 6 months, with 20% serofast, and also reported stage-dependent differences: cure highest in primary (87%) and secondary syphilis (85.8%), lower in early latent (62.1%), reflecting our poor response in late latent cases. Younger age (<30 years) and higher baseline RPR titres predicted cure, while multiple sexual partners were negatively associated.[11]

Zhang et al. reported at 12 months: serocure 79.3%, serofast 20.1%, failure 0.6%, with serofast linked to older age and lower baseline RPR titres (≤1:8); molecular subtype 14i/a was strongly associated with serofast.[12] Pastuszczak et al. observed 20% serofast at 6 months, decreasing to 16.7% after retreatment, and 26% at 12 months; lower baseline RPR titres and weak TpN47 antibody reactivity predicted serofast, aligning with our finding that low titres and late latent cases remain serofast.[14] Tong et al. reported serocure 65.6% and serofast 34.4% at 12 months (1:8/1:16); early syphilis had higher cure than late (≤ 1:1 & ≥ 1:32) (OR 2.391), and baseline RPR titres influenced outcomes: 1:1 and 1:2 had higher odds of cure (AOR 2.732, 2.380), while 1:8 or 1:16 had lower cure rates (49–57%).15 Leeyaphan et al. reported 98% serocure and 2% serofast at 12 months; baseline VDRL >1:16 and CD4 >200 predicted serocure, while HIV status and syphilis stage did not affect outcomes.[13] Overall, serological outcomes were influenced by syphilis stage, HIV status, and baseline RPR/VDRL titres, with early stage disease and higher titres predicting serocure, while late latent cases, PLHA, and low titres were more likely to remain serofast.

In our study, early syphilis RPR titres ranged from 1:8 to 1:128, with all achieving serocure within 6 months, except for one early latent case. Late syphilis titres were lower (1:2–1:8). Among the three antenatal mothers, two infants were treated according to Scenario-3 and one according to Scenario-2. Sena et al. showed baseline RPR titre strongly influenced treatment: 62.7% with titres ≤1:32 achieved cure versus 95.2% with titres ≥1:256.11 Zhang et al. reported low baseline titres (≤1:8) predicted higher serofast risk; titres in serofast patients declined but plateaued at low levels (mostly 1:2 at 12 months), with no antenatal outcomes described.[12]

Tong et al. reported similar baseline RPR findings: low titres (1:8 or 1:16) had lower cure rates (49–57%), while 1:1 and 1:2 predicted higher cure.[15] Liu et al. found higher baseline non-treponemal antibody titres (≥1:32) significantly correlated with serocure, whereas lower titres were linked to serofast outcomes; in HIV-negative early syphilis, titres >1:32 conferred over six-fold higher chance of cure. Differences were significant at baseline and 6 months, highlighting baseline RPR as a predictor of treatment response, with low titres possibly reflecting impaired immunity.8 Leeyaphan et al. did not report antenatal outcomes, but higher baseline titres (>1:16) predicted serocure, consistent with our findings.[13] The higher baseline RPR/non-treponemal antibody titres predicted serocure, while lower titres were associated with serofast outcomes, highlighting baseline titres as a key predictor of treatment response across studies.

Limitations

This study was limited by its single-centre design and relatively small sample size, which may restrict generalisability. In addition, the follow-up period was short, which limited the ability to assess long-term serological outcomes.

CONCLUSION

Younger patients showed a higher rate of serological cure than older individuals, although the difference was not significant. Marital status and gender did not influence the treatment response. The serofast state was significantly more frequent in PLHA and in those with late latent syphilis, whereas early syphilis cases achieved higher serocure rates. These findings highlight the importance of stage-specific monitoring and the impact of HIV coinfection. Future multicentre studies with larger sample sizes and longer follow-ups are needed to validate these predictors and improve management strategies.

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