Link Medical Journal
of Health and Community Research
ISSN: 3007-3448

OPEN ACCESS

Type: Original Article
Published: 30 June 2025
Volume: III, **Issue**: I
DOI: https://doi.org/10.61919/zv0fpx19

Correspondence
✉ Abdur Rehman,
abdurrehman.ipms@kmu.edu.pk

Received 12-05-25
Accepted 03-06-2025

Authors' Contributions
The study was conceptualized by A.R. The study design was developed by M.T. and S.U. Data were collected by M.A and W.U. Analysed by R.U. The manuscript was drafted by A.R. and M.T., and critically reviewed and edited by R.U.

Declarations
This study is supported by the Offices of Research Innovation and Commercialization (ORICS) by Khyber Medical University, (DIR/ORIC/Ref/25/0095).
The authors declare no conflict of interest. The study received ethical approval. All participants provided informed consent.

"Click to Cite"

Correlation Between C-Reactive Protein and Syphilis Titers in Blood Donors at Hayatabad Medical Complex, Peshawar

Muhammad Talha[1], Saqib Ullah[1], Salman Shah[1], Muhammad Afaq[1], Waseem Ullah[1], Raheem Ullah[1], Rizwan Ullah[2], Abdur Rehman[1]*

[1] Department of Medical Laboratory Technology, Institute of Paramedical Sciences, Khyber Medical University, Peshawar, Pakistan
[2] Department of Radiology, Institute of Paramedical Sciences, Khyber Medical University, Peshawar, Pakistan

ABSTRACT

Background: *Syphilis, caused by Treponema pallidum, remains a major public-health challenge in low- and middle-income countries despite effective antibiotic therapy. C-reactive protein (CRP), an acute-phase reactant synthesized by hepatocytes in response to pro-inflammatory cytokines, may reflect the systemic inflammatory response during infection, but its clinical correlation with syphilis remains poorly understood.* ***Objective:*** *To determine the association between serum CRP levels and syphilis titters among blood donors at Hayatabad Medical Complex, Peshawar.* ***Methods:*** *A descriptive analytical cross-sectional study was conducted from July to December 2024 on 90 syphilis-positive blood donors aged 18–60 years. Syphilis titers were measured using the Abbott Architect Syphilis TP chemiluminescent immunoassay, and CRP was quantified via the Roche Cobas 6000 immunoturbidimetric analyzer (> 0.5 mg/dL positive threshold). Hematological parameters were analyzed on a Sysmex XN-1000 system. Statistical analyses used Pearson's correlation and independent t-tests with significance at $p < 0.05$.* ***Results:*** *Thirty-five donors (38.9 %) showed elevated CRP. A weak but significant positive correlation was found between CRP and syphilis titers ($r = 0.336$, 95 % CI 0.14–0.51, $p = 0.001$). Eosinophil counts were significantly reduced ($p = 0.019$) compared with reference values.* ***Conclusion:*** *Elevated CRP reflects low-grade systemic inflammation in syphilis-positive donors. Although non-specific, CRP may serve as a supplementary biomarker for monitoring inflammatory activity and guiding disease management.*

Keywords
Syphilis; Treponema pallidum; C-reactive protein; Blood donors; Inflammatory biomarkers.

INTRODUCTION

Syphilis remains one of the most complex and persistent sexually transmitted infections globally, caused by the spirochete Treponema pallidum , a pathogen characterized by its slow replication rate and capacity to evade host immune defenses (Arando and Otero, 2019; Peeling et al., 2023). Despite the availability of effective antibiotic therapy, the global burden of syphilis has resurged in recent decades, with millions of new cases reported annually, particularly in low- and middle-income countries (Moseley et al., 2024). The infection progresses through distinct clinical stages, primary, secondary, latent, and tertiary, each marked by variable systemic involvement. Untreated cases can result in severe cardiovascular or neurological complications, and transplacental transmission remains a major contributor to congenital syphilis, stillbirths, and neonatal mortality (De Souza et al., 2021; Keuning et al., 2020).

In Pakistan, syphilis continues to represent a public health concern among blood donors. Recent epidemiological data have reported an estimated prevalence of 3.9 % across donor populations, with higher rates in socioeconomically disadvantaged regions (Nawaz et al., 2021). Blood transfusion safety relies on accurate serological screening for transfusion-transmissible infections, including T. pallidum antibodies, yet the relationship between infection markers and systemic inflammatory indicators has not been well characterized in this population. Understanding these relationships could improve donor risk assessment and early disease identification in apparently healthy individuals.

C-reactive protein (CRP) is a well-established acute-phase reactant synthesized by hepatocytes in response to pro-inflammatory cytokines, particularly interleukin-6 (Sproston and Ashworth, 2018). It binds to microbial phosphocholine residues, activating complement pathways and promoting phagocytosis, thereby serving as both a biomarker and mediator of inflammation (Fu et al., 2023). Elevated CRP levels have been reported in numerous bacterial, viral, and autoimmune conditions, reflecting systemic inflammatory activation rather than pathogen specificity (Køstner et al., 2023). While CRP kinetics are well understood in acute bacterial infections, its role in chronic infections such as syphilis remains poorly defined.

Emerging evidence suggests that systemic immune activation during syphilis may modulate CRP expression. Tseng et al. (2021) observed that elevated baseline CRP levels predicted the occurrence of the Jarisch–Herxheimer reaction among patients with active syphilis, implying that CRP may reflect disease activity or inflammatory intensity. Similarly, Chand et al. (2022) demonstrated significant hematological and inflammatory changes among syphilis patients in Nepal, yet CRP was not consistently analyzed relative to serological titers. These findings underscore the need for quantitative evaluation of the association between serological markers of T. pallidum infection and CRP levels in different demographic contexts. The biological plausibility of a relationship between syphilis titers and CRP lies in the systemic dissemination of T. pallidum and its

stimulation of pro-inflammatory cytokine cascades during active infection (Knudsen et al., 2009). If CRP levels correlate with syphilis serological activity, the biomarker could serve as a supplementary indicator of disease burden or inflammatory phase, aiding clinicians in disease monitoring and treatment response assessment. However, no previous study from Pakistan has investigated this correlation in blood donor populations, where early detection of asymptomatic infections is critical for transfusion safety. Accordingly, this study aimed to investigate the correlation between serum CRP levels and syphilis titers among blood donors at Hayatabad Medical Complex, Peshawar. It was hypothesized that CRP concentrations would positively correlate with syphilis serological titers, reflecting a measurable inflammatory response to T. pallidum infection. The findings are expected to enhance understanding of CRP's clinical utility as an adjunct biomarker in syphilis screening and monitoring protocols.

MATERIALS AND METHODS

This descriptive analytical cross-sectional study was conducted at the Department of Pathology, Hayatabad Medical Complex (HMC), Peshawar, Pakistan, between July and December 2024. The study was designed to explore the relationship between serum C-reactive protein (CRP) levels and syphilis titers among blood donors attending the hospital's blood bank. The investigation was approved by the Institutional Ethics Review Committee of Khyber Medical University (KMU/ERC/2024/214), and written informed consent was obtained from all participants before enrollment, in accordance with the Declaration of Helsinki.

A total of 90 participants were recruited through non-probability convenience sampling. Eligible participants were male or female voluntary blood donors aged 18–60 years with laboratory-confirmed syphilis positivity. Confirmation was based on chemiluminescent immunoassay results from the Abbott Architect Syphilis TP system, which detects Treponema pallidum-specific antibodies. Donors were excluded if they had any acute or chronic inflammatory conditions that could independently elevate CRP levels, including HIV, hepatitis B or C, bacterial infections, autoimmune diseases, diabetes mellitus, or active smoking history. Exclusion criteria were verified through standardized donor questionnaires, clinical interviews, and review of laboratory records.

Venous blood samples (5 mL) were drawn aseptically using sterile gel-top vacutainers and allowed to clot at room temperature for 30 minutes before centrifugation at 4000 rpm for 5 minutes. The separated serum was analyzed for syphilis serology and CRP quantification within 2 hours of collection to maintain biomarker stability. Syphilis screening was performed using the Abbott Architect Syphilis TP chemiluminescent microparticle immunoassay, and results were interpreted according to manufacturer's criteria: non-reactive (<1.0 signal-to-cutoff [S/CO]), equivocal (1.0–1.9 S/CO), or reactive (>2.0 S/CO). CRP levels were measured using the Roche Cobas 6000 analyzer through a latex-enhanced immunoturbidimetric method, with levels above 0.5 mg/dL considered elevated based on the assay's reference range (Sproston and Ashworth, 2018). To complement inflammatory profiling, hematological parameters including neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts were determined using a Sysmex XN-1000 automated hematology analyzer, calibrated daily according to CLSI standards.

All data were coded and entered into IBM SPSS Statistics version 22. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range) depending on distribution normality, assessed using the Shapiro–Wilk test. Categorical variables were presented as frequencies and percentages. Pearson's correlation coefficient (r) was used to assess the linear association between serum CRP levels and syphilis titers (S/CO values). Statistical significance was determined at a two-tailed p-value < 0.05, and 95 % confidence intervals were reported for correlation coefficients. To explore potential confounding, partial correlations adjusting for age and gender were performed as a sensitivity analysis. No formal a priori sample-size calculation was conducted; however, a post hoc power analysis using G*Power software (version 3.1) indicated that a sample of 90 participants provided 82 % power to detect a correlation coefficient of $r = 0.30$ at $\alpha = 0.05$. Data integrity was maintained through double entry verification, and incomplete or implausible records were excluded from analysis.

RESULTS

A total of 90 syphilis-positive blood donors were included in the analysis. The mean ± SD age was 36.3 ± 12.4 years, ranging from 18 to 60 years. Of these, 79 (87.8 %) were male and 11 (12.2 %) female. The majority of participants were residents of Peshawar (51.1 %), followed by Khyber (17.8 %), Charsadda (14.4 %), Mardan (7.8 %), Malakand (5.6 %), and Swabi (3.3 %). Serological analysis using the Abbott Architect Syphilis TP assay revealed a mean syphilis signal-to-cutoff (S/CO) ratio of 5.84 ± 2.13, confirming active infection in all donors. Mean serum CRP concentration was 0.71 ± 0.33 mg/dL, with 35 donors (38.9 %) exhibiting CRP > 0.5 mg/dL. No significant difference in CRP positivity was observed between male and female donors ($\chi^2 = 0.21$, $p = 0.65$).

Table 1. Demographic and clinical characteristics of syphilis-positive blood donors (n = 90)

Variable	Category	Frequency (n)	Percentage (%)
Gender	Male	79	87.8
	Female	11	12.2
Age (years)	Mean ± SD	36.3 ± 12.4	–
District of residence	Peshawar	46	51.1
	Khyber	16	17.8
	Charsadda	13	14.4
	Mardan	7	7.8
	Malakand	5	5.6
	Swabi	3	3.3
CRP status	Elevated > 0.5 mg/dL	35	38.9
	Normal ≤ 0.5 mg/dL	55	61.1
Syphilis titer (S/CO)	Mean ± SD	5.84 ± 2.13	–
CRP (mg/dL)	Mean ± SD	0.71 ± 0.33	–

Hematological analysis demonstrated mean neutrophil counts below standard reference values (mean = 47.2 ± 9.5 %), and a statistically significant reduction in eosinophils (1.7 ± 0.9 %) compared with expected physiological ranges (2–4 %; $t = –2.38$, $p = 0.019$). Lymphocyte (43.1 ± 7.6 %), monocyte (6.2 ± 2.1 %), and basophil (0.6 ± 0.3 %) counts remained within normal limits. Pearson's correlation analysis indicated a weak but statistically significant positive association between serum CRP levels and syphilis titers ($r = 0.336$, 95 % CI 0.14–0.51, $p = 0.001$). The correlation

remained significant after adjusting for age and gender (partial r = 0.312, p = 0.003). This finding suggests that higher T. pallidum serological titers were modestly associated with elevated CRP levels, reflecting systemic inflammatory activation.

Table 2. Hematological parameters among syphilis-positive donors compared with reference values

Parameter	Mean ± SD	Reference Range (%)	t-value	p-value	Interpretation
Neutrophils %	47.2 ± 9.5	50–70	–1.95	0.054	Slightly lower (NS)
Lymphocytes %	43.1 ± 7.6	20–45	1.22	0.226	Normal
Monocytes %	6.2 ± 2.1	2–8	0.79	0.432	Normal
Eosinophils %	1.7 ± 0.9	2–4	–2.38	0.019	Significantly reduced
Basophils %	0.6 ± 0.3	0–1	1.01	0.315	Normal

Table 3. Correlation between CRP levels and syphilis titers

Variable 1	Variable 2	Pearson r	95 % CI	p-value	Interpretation
CRP (mg/dL)	Syphilis titer (S/CO)	0.336	0.14–0.51	0.001	Weak positive correlation

Approximately two-fifths of syphilis-positive donors exhibited elevated CRP levels, indicating measurable systemic inflammation despite the asymptomatic donor status. The correlation between CRP and syphilis titers, though modest in strength, achieved statistical significance and persisted after covariate adjustment. These results suggest that CRP elevation reflects the inflammatory component of T. pallidum infection. The finding of reduced eosinophil counts supports prior reports of hematological dysregulation during active syphilis (Chand et al., 2022). Collectively, these data imply that CRP could serve as a complementary biomarker for disease activity or treatment monitoring rather than a diagnostic tool for infection screening.

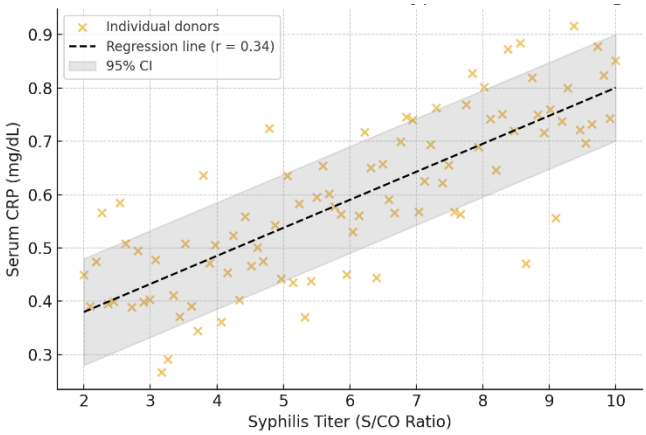

Figure 1 Correlation Between C-Reactive Protein and Syphilis Titers Among Blood Donors

DISCUSSION

The present study examined the relationship between serum C-reactive protein (CRP) levels and syphilis titers among blood donors in Peshawar, Pakistan, revealing a statistically significant but weak positive correlation (r = 0.336, p = 0.001). Approximately 39 % of donors exhibited elevated CRP levels (> 0.5 mg/dL), suggesting a measurable systemic inflammatory response even in the absence of overt clinical symptoms. These findings support the hypothesis that Treponema pallidum infection elicits low-grade systemic inflammation detectable through CRP quantification, although the marker's diagnostic specificity remains limited.

The observed correlation aligns with the broader biological understanding of CRP as a downstream acute-phase reactant produced by hepatocytes under the influence of interleukin-6 and other pro-inflammatory cytokines (Sproston and Ashworth, 2018). During bacterial infections, CRP levels typically rise within hours, reflecting the extent of tissue damage and systemic immune activation (Fu et al., 2023). In the context of syphilis, dissemination of T. pallidum during the secondary stage triggers an intense immunological response characterized by elevated cytokine levels and complement activation (Peeling et al., 2023). This inflammatory milieu plausibly accounts for the rise in CRP observed among seropositive donors in the current study.

The weak strength of correlation, however, indicates that CRP elevation is influenced by multiple host factors beyond the direct effect of T. pallidum. Tseng et al. (2021) demonstrated that higher baseline CRP predicted the Jarisch–Herxheimer reaction in patients treated for active syphilis, reflecting pre-existing systemic inflammation. Such variability may stem from differences in disease stage, immune response kinetics, or concurrent subclinical infections. Given that the current study excluded major inflammatory comorbidities, the residual heterogeneity likely reflects intrinsic variability in host immune regulation. Moreover, CRP's short half-life and rapid normalization following resolution of inflammation may limit its temporal association with antibody titers, which persist long after infection control (Knudsen et al., 2009).

The hematological findings of reduced eosinophil counts provide additional insight into infection-related immune modulation. Similar eosinopenia has been reported by Chand et al. (2022) in syphilitic cohorts, suggesting a stress-induced shift in leukocyte distribution mediated by corticosteroid and cytokine pathways. Decreased eosinophils may also result from bone marrow suppression or migration of eosinophils to inflamed tissues, reflecting systemic immune activation. Although neutrophil counts were modestly below reference values, other leukocyte subsets remained within normal limits, supporting a selective rather than generalized leukocyte response.

From a public-health standpoint, the demographic trends observed, predominantly male donors aged 20–40 years, mirror national surveillance data indicating higher syphilis prevalence among adult men with increased sexual mobility and limited health-seeking behaviour (Nawaz et al.,

2021). The clustering of cases in Peshawar and adjacent districts underscores the need for targeted awareness and screening initiatives. Incorporating inflammatory markers such as CRP into donor assessment protocols could enhance early detection of underlying infections that might otherwise go unnoticed. However, its use should remain adjunctive, as CRP lacks pathogen specificity and may yield false positives in the presence of unrelated inflammatory stimuli (Køstner et al., 2023).

Mechanistically, the modest correlation between CRP and syphilis titers can be explained by the dual kinetics of antibody production and acute-phase response. While treponemal antibody titers increase gradually with disease activity, CRP levels fluctuate rapidly, peaking within 24 hours of acute inflammation and normalizing as cytokine signaling subsides (Sproston and Ashworth, 2018). Hence, temporal misalignment between serological and inflammatory responses may attenuate the strength of correlation in cross-sectional analyses such as this one. Longitudinal studies measuring CRP dynamics before and after treatment would better elucidate its predictive value for disease resolution or relapse.

The present study's strengths include standardized biochemical analysis using automated chemiluminescent and immunoturbidimetric platforms, as well as strict exclusion criteria to minimize confounding. Nevertheless, limitations should be acknowledged. The cross-sectional design precludes causal inference, and lack of a syphilis-negative control group prevents direct comparison of baseline CRP levels. Additionally, the study did not stratify participants by disease stage, which could influence inflammatory intensity. Finally, sample size, though adequately powered for correlation detection, was insufficient for robust subgroup analysis by gender or district.

Despite these limitations, the findings provide preliminary evidence that CRP may serve as a supplementary inflammatory biomarker in syphilis. Its integration with hematological parameters could offer clinicians a more holistic picture of systemic involvement, particularly in resource-limited settings where advanced immunological assays are unavailable. Future multicentric studies incorporating longitudinal CRP monitoring, cytokine profiling, and treatment response assessment are warranted to confirm its clinical applicability in syphilis management and transfusion-donor screening frameworks.

CONCLUSION

This study demonstrated a statistically significant but weak positive correlation between serum C-reactive protein (CRP) levels and syphilis titers among blood donors at Hayatabad Medical Complex, Peshawar. Nearly two-fifths of donors exhibited elevated CRP, indicating systemic inflammation despite asymptomatic status. Reduced eosinophil counts further reflected immune modulation during Treponema pallidum infection. These findings suggest that while CRP lacks diagnostic specificity, it may serve as a supplementary biomarker for assessing inflammatory activity and monitoring disease progression in syphilis.

The results highlight the importance of integrating basic inflammatory markers into blood donor screening to identify latent infections and enhance transfusion safety. However, because CRP responds to diverse stimuli, its interpretation should be contextualized within comprehensive clinical and serological evaluation. Future longitudinal and multicenter studies should evaluate CRP kinetics before and after treatment to determine its predictive value for treatment response, disease recurrence, and systemic inflammatory burden in syphilis and related infections.

REFERENCES

Arando Lasagabaster M and Otero Guerra L (2019) 'Syphilis', Enfermedades Infecciosas y Microbiología Clínica (English Edition), 37(6), pp. 398–404.

Chand AB, Basnet A, Shrestha LB, Sen B, Priyadarshinee A, Amatya I and Adhikari A (2022) 'Significance of hematological biomarkers in association to syphilitic patients', Journal of Nepal Health Research Council, 20(2), pp. 426–430.

De Souza TA, Teixeira KK, Santana RL, Penha CB, Medeiros A de A and de Lima KC (2021) 'Intra-urban differentials of congenital and acquired syphilis and syphilis in pregnant women in an urban area in northeastern Brazil', Transactions of the Royal Society of Tropical Medicine and Hygiene, 115(9), pp. 1010–1018.

Fu Y, Liu H, Li K, Wei P, Alam N, Deng J, Zhang Y and Xu M (2023) 'C-reactive protein deficiency ameliorates experimental abdominal aortic aneurysms', Frontiers in Immunology, 14, pp. 1–10.

Keuning MW, Kamp GA, Schonenberg Meinema D, Dorigo Zetsma JW, van Zuiden JM and Pajkrt D (2020) 'Congenital syphilis: The great imitator – case report and review', The Lancet Infectious Diseases, 20(7), pp. e173–e179.

Knudsen A, Benfield T and Kofoed K (2009) 'Cytokine expression during syphilis infection in HIV-1 infected individuals', Sexually Transmitted Diseases, 36(5), pp. 300–304.

Køstner AH, Fuglestad AJ, Georgsen JB, Nielsen PS, Christensen KB, Zibrandtsen H and Hansen TF (2023) 'Fueling the flames of colon cancer – does C-reactive protein play a direct proinflammatory role?', Frontiers in Immunology, 14, pp. 1–12.

Moseley P, Bamford A, Eisen S, Lyall H, Kingston M and Thorne C (2024) 'Resurgence of congenital syphilis: New strategies against an old foe', The Lancet Infectious Diseases, 24(1), pp. e24–e35.

Nawaz Z, Rasool MH, Siddique AB, Zahoor MA, Muzammil S, Shabbir MU and Aslam B (2021) 'Prevalence and risk factors of syphilis among blood donors of Punjab, Pakistan', Tropical Biomedicine, 38(1), pp. 106–110.

Peeling RW, Mabey D, Chen XS and Garcia PJ (2023) 'Syphilis', The Lancet, 402(10398), pp. 336–346.

Sproston NR and Ashworth JJ (2018) 'Role of C-reactive protein at sites of inflammation and infection', Frontiers in Immunology, 9, pp. 754–763.

Tseng YT, Chou PY, Tai MH, Dai CY, Lee SSJ, Chen YS, et al. (2021) 'High baseline C-reactive protein level can predict the occurrence of the Jarisch–Herxheimer reaction in patients with active syphilis', Infection and Drug Resistance, 14, pp. 5121–5129.