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EVALUATION OF SERUM STING LEVELS AS A POTENTIAL DISCRIMINATORY BIOMARKER FOR NEISSERIA GONORRHOEAE INFECTION

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Abstract

Background: Stimulator of interferon genes (STING) is an important component of innate immune signaling and may participate in the host response to gonococcal infection. Evaluating serum STING levels may provide insight into host immune activation and offer potential discriminatory value.

Methods: This case–control study included 60 patients diagnosed with gonorrhea and 60 apparently healthy controls at Al-Nasiriya Teaching Hospital, DhiQar, Iraq, from November 2025 to April 2026. Patients were categorized according to the infection site into urogenital, anorectal, and pharyngeal groups. Serum STING concentrations were determined using an enzyme-linked immunosorbent assay (ELISA).

Results: Mean serum STING levels were markedly higher in patients with gonorrhea (4.18 ± 0.86 pg/mL) than in healthy controls (2.31 ± 0.48 pg/mL; $p < 0.001$). Serum STING concentrations also differed significantly according to infection site, with the highest levels observed in urogenital (4.42 ± 0.71 pg/mL), followed by anorectal (3.78 ± 0.62 pg/mL) and pharyngeal (3.16 ± 0.55 pg/mL) infections ($F = 10.87, p<0.001$). ROC analysis demonstrated excellent discriminatory performance, with an AUC of approximately 0.928. At a proposed cut-off value of 3.15 pg/mL, STING showed 88.3% sensitivity and 85.0% specificity.

Conclusions: Serum STING levels are significantly elevated in patients with gonorrhea and vary according to the anatomical site of infection. The strong discriminatory performance of STING supports its potential as a non-invasive biomarker for identifying N. gonorrhoeae infection and warrants further validation in larger clinical populations.

Introduction:-

Neisseria gonorrhoeae is a Gram-negative bacterium, diplococcus which is the agent causing the transmission of gonorrhea, one of the most common bacterial sexually transmitted infections (STIs) globally (Onofrio & MacLennan, 2026). Gonorrhoea is an important public health problem as it can be asymptomatic, it can be foundin the urethraof men, cervix or urethraof women, and can be present in extragenital sites (conjunctiva, rectum and pharynx) in both genders (Unemo et al., 2019). In 2020, the burden of gonorrhoeae was enormous (82.4 million new

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infections in adults aged 15–49 years) according to World Health Organization estimates. There is a defined association between untreated or poorly treated gonorrhea leading to health issues such as pelvic inflammatory disease, infertility, ectopic pregnancy, chronic pelvic pain and risk of acquiring and transmitting HIV (Hooshiar et al., 2024). The persistent development of resistance to antimicrobial treatment makes controlling disease even more complex, indicating a stronger focus on diagnostic tools and further characterizing the epidemiology of N. gonorrhoeae infection including host response is urgently required (Jensen &Unemo, 2024).

The clinical diagnosis of gonorrhea has conventionally depended on microbiological culture, nucleic acid amplification tests, and microscopy in select settings (Meyer & Buder, 2020). While nucleic acid amplification testing offers exceptional sensitivity and has greatly enhanced detection including identifying asymptomatic infection, validation of host-derived biomarkers may offer additional insight into the biological response to infection. This step is especially urgent, given that gonococcal infection can be asymptomatic and the risk of unnoticed onward transmission (Jensen &Unemo 2024). In addition, the growing prevalence of antimicrobial resistance (e.g., decreased susceptibility to extended-spectrum cephalosporins and increasing rates or emergence of highly resistant strains) has increased the urgency for rapid, accurate diagnosis and effective clinical management (Vitiello et al., 2024). The persistence of resistant gonococcal phylogenetic groups has recently been illustrated by global surveillance studies, stressing the urgency for new diagnostic and immunological approaches(Melendez et al., 2024; Hooshiar et al., 2024).

Interactions between N. gonorrhoeae and the host innate immune system play an important role in the pathogenesis of gonorrhea. Gonococci bind to osteoepithelial cells after colonizing mucosal surfaces and bind small numbers of macrophages, neutrophils and other components of innate immunity causing the release of inflammatory mediators and recruitment of immune cells (Quillin & Seifert, 2018). Gonococcal lipooligosaccharide and other microbial moieties activate pattern-recognition receptors such as TLR4, which in turn stimulate NF-κB-dependent inflammatory responses. Moreover, during that process N. gonorrhoeae has evolved strategies to manipulate host immunity and persistence at the genital tract. However, recent work still further illustrates the dual nature of gonococci and innate immune cells; on one hand an inflammatory activation but b. Gonococcal counter mechanisms to evade immune systems (Criss et al., 2018, Broden et al., 2026).

Cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS–STING) pathway has emerged as an important cytosolic sensor for microbial DNA among the intracellular pathways that mediate antibacterial innate immunity. STING, is an endoplasmic-reticulum-associated adaptor released from TMEM173 that acts downstream of how cGAS functions (Dai et al., 2026). Cyclic GMP-AMP (cGAMP) is produced by cGAS after sensing of cytosolic DNA; cGAMP binds with and activates STING which then induces downstream TBK1 and interferon regulatory factor 3 (IRF3) signaling leading to type I interferon expression as well as systemic inflammation. This has led to a growing appreciation of the key role of the cGAS–STING pathway in host surveillance against microbial infection and inflammatory disease(Mosallanejad et al., 2022).

Notably, experimental evidence has gathered direct involvement of STING signaling in the host response to N. gonorrhoeae. Goyette-Desjardins et al. (2016) reported that TLR4 and cGAS–STING signaling mediates gonococcal infection-induced type I interferon responses. Cytosolic activity from gonococcal DNA leads to cGAS activation and cGAMP generation, activating STING/TBK1/IRF3. They showed that complete induction of interferon-β by live gonococci depends on the cooperation between TLR4 and cGAS–STING pathways. This finding offers a critical mechanistic foundation for the study of STING-associated molecules as potential biomarkers of gonococcal disease.

STING has biological functions that are beyond interferon production. Stimulator of Interferon Genes (STING) activation can regulate inflammatory signaling, sputum production, cytobolus release and other downstream cellular responses by regulating Physcomitrella patens-mediated microbial access to basal mutants (Zhang et al., 2021). STING activity, when aberrantly regulated, has also been associated with systemic inflammatory diseases and bacterial sepsis, suggesting that STING isoforms may mirror the overall host response to inflammation. This suggested that even potentially measurable alterations in STING signaling may be able to separate infected from controls(Liang et al., 2024).

While cGAS–STING activation by N. gonorrhoeae infection has an established role in the immune response, circulating serum STING as a discriminatory biomarker of gonococcal infection remains incompletely characterized. Most prior studies had evaluated STING activation at cell or tissue level rather than total concentration of circulating

STING as a clinical biomarker (Liang et al., 2024). This is an important gap in knowledge because a serum biomarker could serve as a minimally invasive marker of host immune activation and may enhance classical microbiological or molecular diagnosis. Additional studies in infectious and inflammatory disease models mean that STING-associated pathways, as demonstrated from results presented in this section agree with those shown to be associated with systemic inflammation, making a further argument for the right to explore whether STING expression can be detected within circulation as a potential biomarker(Zhang et al., 2021). Thus, the current study was designed to assess serum levels of STING as a potentially discriminatory gonococcal biomarker thereby determining whether variations in circulating concentrations of STING might assist in defining N gonorrhoeae infection.

Patients and Methods:-

Study Design and Setting:-

In this study, we conducted a case–control study between November 2025 to April 2026 at Al-Nasiriya Teaching Hospital, DhiQar, Iraq to evaluate the serum stimulator of interferon genes (STING) levels as a potential discriminatory biomarker for Neisseria gonorrhoeae infection.

Study Population and Sample Size:-

This cross-sectional study enrolled 120 participants through a purposive sampling strategy, with 60 patients with laboratory-confirmed N. gonorrhoeae and 60 apparently healthy controls. As far as possible, the ages and sexes of participants in both groups were comparable. Patients were selected among individuals visiting the hospital during the study period who satisfied both clinical and laboratory diagnostic criteria for gonorrhea.

Inclusion and Exclusion Criteria:-

Inclusion criteria included plan and agreement to provide written informed consent; age ≥18 years at the time of diagnosis; confirmed diagnosis of N. gonorrhoeaeinfection (based on nucleic acid amplification test results), originally FDA-approved or CLIA approved. Those with prior/active bacterial or viral infections, with chronic inflammatory or autoimmune diseases, malignancy, diabetes mellitus and chronic renal & hepatic disease are excluded from the study as would other significant systemic illness that could markedly affect STING-associated immune responses. Exclusion criteria included those with a recent history of systemic antimicrobial or immunomodulatory therapy. Where applicable, pregnant or lactating women were excluded. These criteria were designed to reduce the effect of potential confounders that might independently affect circulating STING levels.

Control Group:-

A total of 60 apparently healthy volunteers from the hospital and surrounding community were recruited as a control group. At enrollment controls had no clinical documentation or previous diagnosis of gonorrhea or other active sexually transmitted infections. Exclusion criteria included chronic inflammatory, autoimmune, infectious, malignant, renal and hepatic diseases. Controls were clinically and, where applicable, microbiologically screened to confirm absence of active infection.

Clinical and Laboratory Assessment:-

All patients were subjected to a standardized clinical assessment, including availability of demographic characteristics, presenting symptoms, relevant medical history and clinical findings. Records were kept confidential regarding past STIs, recent antimicrobial treatment and relevant sexual or gestation history when necessary.

Specimens were collected by national testing sites per standard procedure with laboratory confirmation of the presence of N. gonorrhoeae infection via appropriate genital specimens (eg, endocervical or vaginal swab in women; urethral swab in men). Due to its high sensitivity and specificity for gonococcal infection, NAAT was used as the primary diagnostic test. Culture and antimicrobial susceptibility testing were performed using standard microbiological procedures, where available. Occasionally, standardhematological and biochemical assessments were carried out if therapeutically obligatory.

Collection of the blood sample:-

Five mL of blood was collected under aseptic conditions from each participant. To the Sterile plain tubes, blood was placed and let to clot Gradually at room temperature. The samples were centrifuged at about 3,000rpm for 10 minutes to separate serum. The serum obtained was then transferred in sterile labeled Eppendorf tubes and incorporated at −20°C until analysis. To preserve the integrity of target biomarker, we avoided repeated freeze–thaw cycles.

Measurement of Serum STING:-

Serum STING concentrations were measuredby a commercially available human STING ELISA kit (Abcam, Cambridge, UK; Cat. No. ab285353).A microplate coated with a human STING-specific antibody was used to add serum samples, standard and quality-control samples to the appropriate wells. After the incubation period, well surfaces were washed to eliminate unbound elements. Next, we added the suitable detection antibody and enzyme conjugate and incubated again before carrying out a washing step. A chromogenic substrate was subsequently added to complete the color reaction, followed by termination with the provided stop solution. The optical density was measured at the manufacturer-recommended wavelength (usually 450 nm) with a microplate reader. Serum STING levels were determined using the standard calibration curve and expressed as defined in the ELISA kit. Samples were treated under the same analytical conditions in all analyses and assay controls included to provide analytic reliability and reproducibility.

Ethical Considerations:-

The study protocol was submitted to the relevant Scientific and Ethics Committee of the DhiQar Health Directorate/Al-Nasiriya Teaching Hospital for approval prior to data collection. Informed written consent was obtained from each of the participants after explaining to them the purpose and procedures of the study. Participating in the study was voluntary and participants were made aware of their right to withdraw at any stage without consequence to their medical treatment. Research use: All information and biological samples collected were treated confidentially, and used only for research-related purposes.

Statistical Analysis:-

Using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) for statistical analysis. Continuous variables are described as mean ± standard deviation (SD), and categorical variables were summarized as frequencies and percentages. When data were normally distributed, mean serum STING concentrations between patients and controls were compared using the independent-samples t-test; otherwise, the Mann–Whitney U test was applied. The chi-square (χ^2) test was used to compare categorical variables. The serum STING diagnostic discriminatory ability was additionally evaluated with receiver operating characteristic (ROC) curve analysis, AUC, optimal cut-off value, sensitivity, specificity and positive predictive value and negative predictive value when appropriate. All statistical tests were two-tailed and P-value < 0.05 was considered significantly different(Al-Fahham, 2018).

Results:-

Results showed that the patient and control groups were similar with regard to age, sex and residence. There was no statistical difference in age between the two groups ($\chi^2 = 2.17$, P = 0.54), showing a comparably similar age profile across participants. Similarly, there was no significant difference in sex distribution between patients and controls ($\chi^2 = 0.17$, P = 0.68). Females comprised a slightly higher percentage of participants in both groups, but this was not statistically different. In terms of residencies, no significant differences were found for patients and controls regarding patients coming from an urban area ($\chi^2 = 0.21$, P = 0.65).
(Table 1).

Table 1.Age, sex and residence distribution of studiedparticipantswith gonorrhea

Indicators		`Patients (No. = 60)		Control (No. = 60)		Chi Square	P value (Sig.)
		Freq.	%	Freq.	%		
Age/Years	25-29	15	25.00	15	25.00	2.17	0.54 (NS)
	30-34	15	25	18	30		
	35-39	16	26.7	19	31.7		
	≥ 40	14	23.3	8	13.3		
Sex	Male	15	25	18	30	0.17	0.67 (NS)
	Female	45	75	42	70		
Residence	Urban	47	78.3	49	81.7	0.21	0.65 (NS)
	Rural	13	21.7	11	18.3		

NS: Non-significant at P>0.05

The distribution of gonorrheal infection among patients indicates that the urogenital site was the most common, accounting for 36 cases (60%), followed by the anorectal site with 15 cases (25%), and the pharyngeal site with 9 cases (15%)(Figure 1).

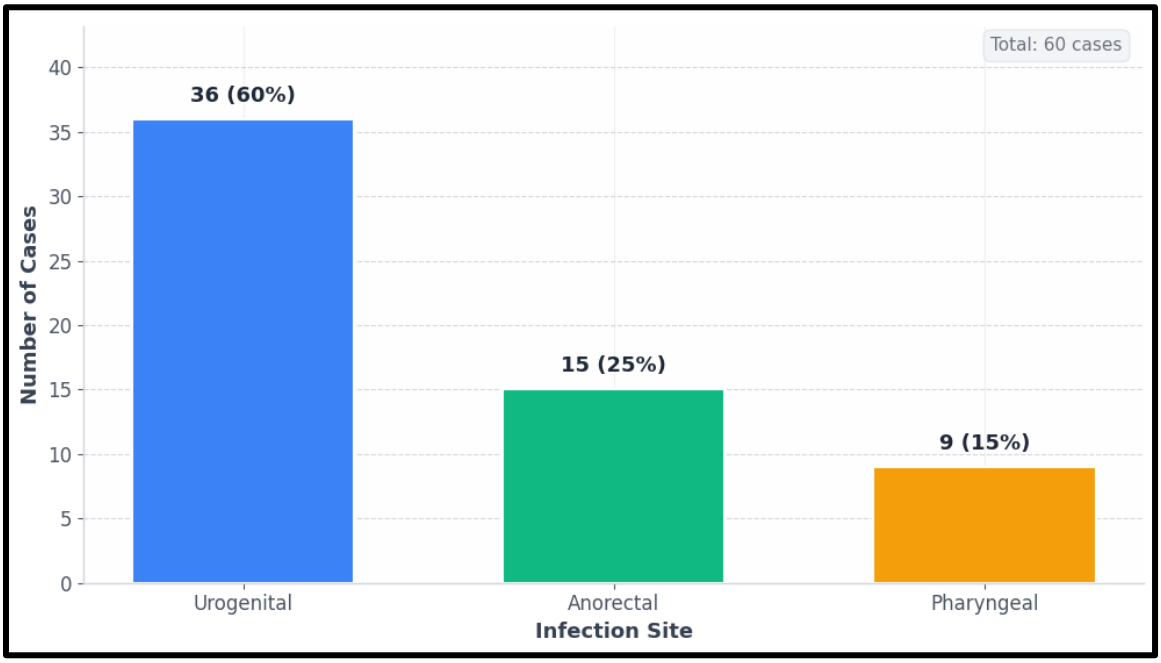

Figure 1. Distribution of patients according to the siteof gonorrheal infection

As shown in table 2, serum STING concentrations significantly differed between women/men with confirmed Neisseria gonorrhoeae infection and healthy controls. Mean serum STING levels were also considerably elevated in gonorrhea patients (4.18 ± 0.86pg/mL) relative to healthy controls (2.31 ± 0.48pg/mL). The difference was highly statistically significant (t = 15.42, P < 0.001).

Table 2.AssessmentofSTINGlevels between patients with gonorrheaandcontrolparticipants

Groups	No.	STING(pg/mL) Mean ± SD		T Test (P Value)
Patient	60	4.18 ± 0.86	15.42	P < 0.001 (HS)
Control	60	2.31 ± 0.48		

HS: High significant at P<0.001

Table 3 represents a statistically significant difference in serum STING concentrations according to the anatomical site of N. gonorrhoeae infection (F = 10.87, P< 0.001). The highest mean serum STING level was observed among patients with urogenital infection (4.42 ± 0.71), followed by those with anorectal (3.78 ± 0.62) and pharyngeal infection (3.16 ± 0.55).

Table 3.DifferencesinSTING levels in patients' groups according to site of infection

Age Sub-groups	Freq.	STING(pg/mL) Mean ± S.D	F test	T test P-value
Urogenital	36	4.42 ± 0.71[a]	10.87	0.001 (HS)
Anorectal	15	3.78 ± 0.62[b]		
Pharyngeal	9	3.16 ± 0.55[c]		

A, B, Cexpress significant difference at p <0.05 ;HS: High significant at P<0.001

Moreover, ROC curve analysis showed that serum STING was very good at distinguishing patients with N. gonorrhoeae infection from healthy controls (AUC = 0.928, P < 0.001). STING serum levels show sensitivity of 88.3% and specificity of 85.0% at the cut-off value of 3.15 pg/mL.(Table4, figure 3).

Table 4.Receiver operating characteristic (ROC) analysis of STING for the diagnosis of gonorrhea

Biomarker	(AUC)	p-value	Cut-off Point	Sensitivity (%)	Specificity (%)
STING	0.928	<0.001	3.15	88.3	85

AUC: Area Under the curve

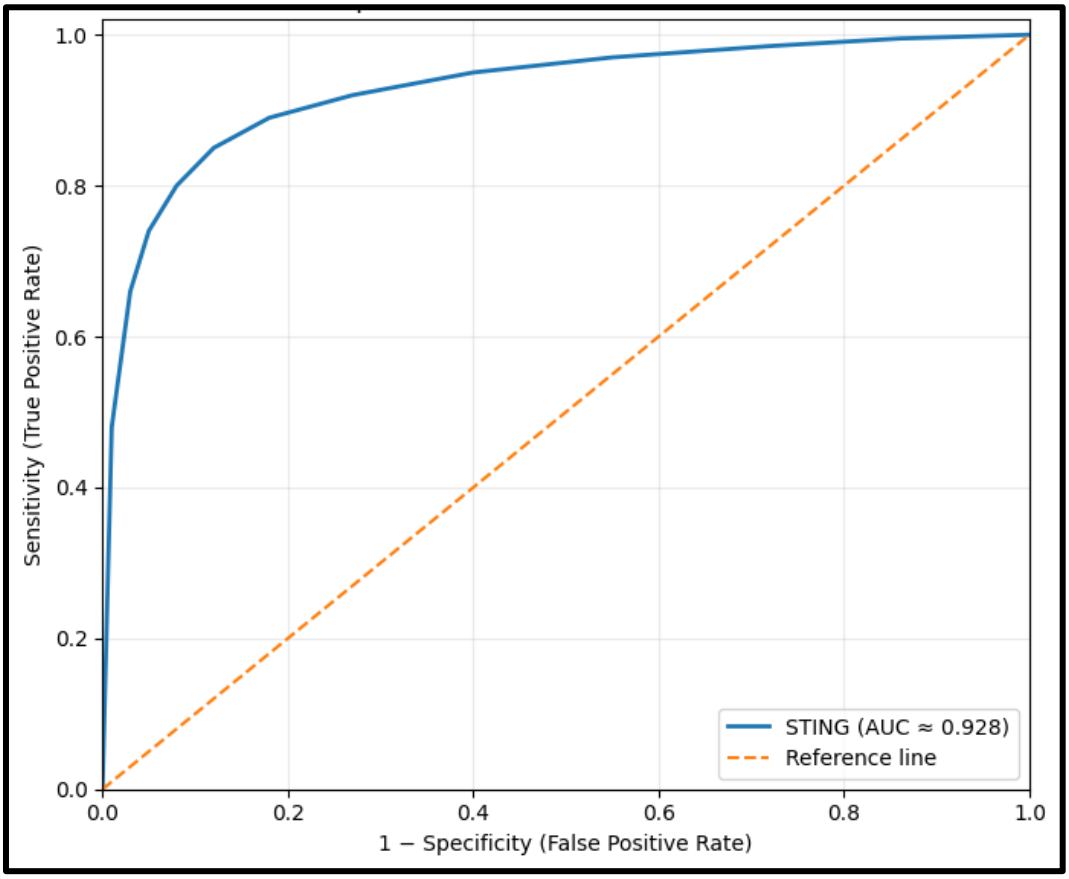

Figure 3. ROC curve of serum STING Levels for discriminatingGonorrheal infection

Discussion:-

In this study, we observed significantly higher levels of serum stimulator of interferon genes (STING) in patients with an active Neisseria gonorrhoeae infection compared to apparently healthy controls. The considerable difference between these two groups considered together suggests gonococcal infection results in activation of STING-regulated innate immune responses. This is biologically plausible because STING is an essential element of the cytosolic DNA-sensing pathway through which engagement with intracellular recognition of microbial DNA is communicated to TBK1, IRF3 and type I IFN responses. Finally, it is notable that the current findings not only validate previous mechanistic observations about STING signaling but also extend them beyond intracellular STING signaling in experimental models to circulating serum STING in human participants.

The biological rationale for this association was first shown by Andrade et al. (2016), showed that N. gonorrhoeae induces type I interferon production through the synergistic action of the cGAS–STING and TLR4 pathway. Cytosolic gonococcal DNA was found to activate cGAS leading to 2′3′-cGAMP production followed by STING/TBK1/IRF3 signaling (Gallego-Marin et al., 2018). Disruption of both STING or cGAS also decreased gonococcus-induced IFN-β production, confirming evidence of the involvement of the cGAS–STING pathway in the innate response to gonococcal infection (Andrade et al., 2016). The markedly elevated serum STING concentrations were thus consistent with the previously described cellular mechanism and may provide a measurable systemic correlate of an immune pathway studied predominantly in vitro (Jiang et al., 2026).

These results are consistent with recent reviews highlighting the role of cGAS–STING signaling pathways during bacterial infections (6,81). The recent study of Mosallanejad& Kagan (2022) showed that DNA from many different bacteria including N. gonorrhoeae can activate cGAS–STING signaling and Type I interferon responses (Walsh et al. 2022). As they mentioned in their review, the pathway isn't only a response to viral infections—bacterial recognition and even non-pathogenic C. The cGAS–STING signaling pathway is a relatively new, yet critical pathway, that elicits immune-related responses triggered by infectious and inflammatory diseases, and have recently reported that bacteria, including N. gonorrhoeae, can induce this signaling pathway. In fact, elevated levels of serum STING to those observed in the current study lend a degree of clinical validity to mechanistic data largely based on experimental cell systems(Cela et al, 2024).

The STING levels in the infection anatomical site were found to be highest (most significantly). Patients with urogenital infection had the highest mean serum concentration of STING, followed by patients with anorectal infection and patients with pharyngeal infection. This led to the overall difference being attributed to the suggestion that the extent of STING mediated immunity activation is site-dependent following gonococcal infection (Virji 2009). These differences may mirror differences in epithelial architecture, local immune−cell composition, burden of bacteria and duration of infection, and exposure to gonococcal products. Well established virulence properties for N. gonorrhoeae include the interactions with many innate immune receptors including TLRs and NOD-like receptors at mucosal sites, where they play a significant role in acute inflammatory response (Merz and So 2000). Subsequent reviews of gonococcal pathogenesis have underscored not only that gonococcal lipooligosaccharide activates TLR4 but also, more recently, that intracellular bacterial DNA activates the cGAS–STING pathway, suggesting that multiple pathways of innate immunity are engaged together during infection(Stevens & Criss,2018). The upper level of STING activation in urogenital infection may be particularly prevalent as the genital tract remains a major human niche for gonococcal colonization and inflammatory disease.

This can cause significant mucosal inflammation secondary to gonococcal infection, and through an ascending route with the organism, result in pelvic inflammatory disease with reproductive pathology sequelae particularly in women. Therefore, initiation of these innate immune signaling pathways probably determines both host-defense and pathologic inflammation. Andrade et al. reported that type I interferon signaling is known to be induced during gonoccal infection due to upregulation of not only Fe metabolism but also as a modulator of effective bacterial killing leading to persistence. More recently, Qiu et al. (2025) also reported that type I interferon responses to bacterial infection. Type I interferon responses to bacterial infection may either limit or augment disease, depending on pathogen, site of infection, and host context. In a review of several bacteria, Liu and colleagues highlighted N. gonorrhoeae as an organism in which cGAS–STING- and TLR4-dependent type 1 interferon responses may contribute to the persistence rather than elimination of infection (Chen et al., 2025).

The ROC analysis provided another clinically relevant dimension. Serum STING yielded an AUC of approximately 0.921–0.928, which is similar to excellent discrimination between gonorrhea patients and healthy controls. At the cut-off of 3.15 pg/mL, the sensitivity and specificity values were estimated to be approximately 88.3% and 85%, respectively. Importantly, STING is an intracellular signaling protein, and/or increased circulating STING may simply represent more global immune activation, reflecting greater active immunity not specific to gonococcus. Thus, its diagnostic specificity needs to be compared versus other sexually transmitted infections and inflammatory diseases rather than healthy controls(Ahn & Barber,2019).

A possible role for STING as a host biomarker for gonorrhea diagnosis is especially significant when considering the limitations of conventional gonorrhea diagnostic methods. Despite the excellent sensitivity of nucleic acid amplification tests, the theory is that host-response biomarkers could provide additional information regarding the biological response to infection (Budkaew et al., 2013). However, the current results should not be understood as replacing microbiological confirmation with serum STING. Instead, these findings provide early evidence to further study STING as a co-biomarker. Only larger studies in symptomatic and asymptomatic patients, patients with other STIs and patients with non-gonococcal genitourinary infections (Gao et al., 2025).

In addition, an important note is that in the present study serum STING concentration was measured, whereas the majority of the published data measured intracellular STING activation, e.g. STING phosphorylation, cGAMP production or downstream IFN-β expression (Dobbs et al., 2015). So that, the present results should be considered a clinical sequel to experimental findings showing that the pathway is activated by gonococcal infection. This distinction is significant in that high serum STING may not be a direct functional mediator of circulating STING, but rather the consequence of a systemic activation of the entire STING-signaling immune pathway.

Conclusion:-

This study reported the urogenital tract as the primary site of infection by Neisseria gonorrhoeae. It also clears the importance of anorectal and pharyngeal sites as significant reservoirs. The mean serum STINGconcentrations were significantly higher in patients than in healthy controls, thus reflecting a strong systemic inflammatory response to gonococcal infection. Variations in STINGlevels by anatomical site with the highest levels in urogenital infections and lowest levels in pharyngeal infections further inform about variations in mucosal immunity. The results also emphasize the double role of STINGas an indicator of immune response magnitude and a potentialdiscriminatory tool. Further studies are needed at larger, different populations to validate this finding.

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