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Evaluation of Advanced Immune Markers (TLR4 and sTREM-1) among three Strains of Escherichia coli

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ABSTRACT

These Escherichia coli strains (Uropathogenic - UPEC, Enteroaggregative – EAEC and Enterotoxigenic ETEC) are major pathogens involved in urinary tract infections, diarrhea diseases and systemic infections. They become pathogenic through adhesion factors, toxin synthesis and tissue colonization, inducing strong innate immune reactions. Toll-like receptor 4 (TLR4) and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) are important immune mediators representing both host recognition of bacterial moieties and further amplification of inflammation. In the present study we aimed to assess serum concentrations of TLR4 as well as sTREM-1 in patients infected with three distinct E. coli serotypes in comparison to healthy controls. Patients and methods A total of 65-cases (confirmed cases due to E. coli) were included at Hilla Teaching Hospital, Babylon/Iraq, over the period from March to September 2025 in addition to 50 apparently healthy subjects as controls. Exclusion criteria were recent antibiotic or anti-inflammatory treatment, chronic systemic diseases, pregnancy and lactation. Peripheral venous blood samples were obtained, the serum TLR4 and sTREM-1 levels in both groups were determined by ELISA. Results Serum levels of TLR4 (mean ≈ 5.8 ng/mL) and sTREM-1 (mean ≈ 152 pg/mL) were significantly raised in infected patients as compared to the controls ($p < 0.05$). Within strains, UPEC-infected patients had the greatest while EAEC- and ETEC-infected patients had lower responses; these findings suggest strain-specific differences in host immune activation. There were no important differences in experimental factors by sex or residence. These findings demonstrate that TLR4 and sTREM-1 are strong markers of innate immunity activation in E. coli infection, which could be used as additional biomarkers to assess host inflammatory response, follow disease activity and potentially differentiate between strain dependent pathogenic profiles.

INTRODUCTION

Escherichia coli (E. coli) stands at an elegant crossroads of mutualism and pathogenesis, whereby the genome of most strains reflects a harmless intestinal commensal, yet strains representative of specific pathotypes (e.g., uropathogenic E. coli; UPEC, enterohemorrhagic E. coli) utilize disparate virulence strategies that potently stimulate divergent immune responses in their hosts. Accordingly, an understanding of how the host detects and amplifies signals initiated by different E. coli strains is important for explaining variation in clinical outcomes (asymptomatic carriage, localized infection, systemic sepsis) and developing targeted diagnostics and treatments (Leatham-Jones et al., 2022).

Amon these defense strategies, two innate immune constituents have emerged as long-lasting candidates for the above response: toll-like receptor 4 (TLR4) which is known to be activated by the Gram-negative lipopolysaccharide (LPS) and triggering receptor expressed on myeloid cells-1 (TREM-1), and its soluble counterpart sTREM-1, an enhancer of inflammation during

bacterial infection. Taken together, this TLR4 and TREM-1 create an axis that both drives and enhances inflammatory cascades in the presence of E. coli-associated molecular patterns; therefore, these are novel and highly-relevant markers when comparing host responses to distinct bacterial strains (Heine et al., 2022; Olson et al., 2016).

TLR4-dependent sensing of E. coli LPS is a prototypical proximal event in innate immunity; ligation of the TLR4/MD-2 complex rapidly leads to engagement of MyD88 dependent and TRIF dependent pathways, ultimately activating NF-κB, producing cytokines and recruiting neutrophils and monocytes. Recent studies have helped sharpen our understanding of TLR4 beyond being just a sensor of LPS: that TLR4 expression and downstream signalling mediate epithelial expulsive mechanisms (which are important in UTIs), orchestrate crosstalk with the adaptive immunity response and can be modulated by surface structures and secreted effectors of bacteria, leading to strain specific differences in host outcomes. Such subtle roles underscore the need to quantitate TLR4 expression or activation, rather than focusing only on presence/absence, when examining immune recognition of multiple E. coli strains (Whelan et al., 2023; Heine et al., 2022).

TREM-1 and its soluble ligand, sTREM-1, are important enhancers of the TLR-induced inflammatory response. TREM-1 is expressed in its soluble form (sTREM-1) in plasma and other body fluids as the cleaved molecule seems to reflect LPS and bacterial stimuli, suggesting that the receptor is upregulated on neutrophils, monocytes after LPS or microbial challenge; its co-stimulation with TLR4 can be significantly increased in pro-inflammatory cytokines production. In particular, clinical and experimental data collected since 2016 show that levels of sTREM-1 correlate with infection severity in bacterial pneumonia and sepsis, and fine tuning of the TREM-1 pathway can attenuate harmful hyperinflammation without interfering with pathogen clearance (Jiang et al., 2020). With its multiple applications as a potential diagnostic marker or target for therapy, sTREM-1 is an attractive molecule worth further studying. For studies that contrast the host response to different E. coli strains, measuring sTREM-1 would reflect the extent of additional inflammatory amplification beyond TLR4 alone (Siskind et al., 2022).

Comparative researches combining bacterial genotyping (e.g., virulence gene profiles, fimbrial types, capsule variant) with assessment of host markers such as TLR4 and sTREM-1 are especially useful. For example, uropathogenic E. coli (UPEC) encode adhesins and a process for forming intra-cytoplasmic bacterial communities that can attenuate epithelial TLR4 responses and elude clearance to cause persistent infections exhibiting unique inflammatory patterns; these strain-specific adaptations provide a plausibly mechanistic basis for phenotypic variation in host marker levels found across clinical populations with varying severity of illness (Olson et al., 2016). Hence, a comparative approach including both strain characteristics and host receptor/soluble marker dynamics should allow to unravel why some E. coli isolates trigger high levels of systemic inflammation (high sTREM-1, high TLR4 activation) whereas others induce dampened or only restricted responses (Whelan et al., 2023).

In view of targeted therapy and precision diagnostics, a systematic detection for TLR4 and sTREM-1 on broad strains of E. coli have three advantages: first, explore whether these two indicators are promising biomarkers to assess the etiology of E. coli; secondly; detect multiple serotypes of E. pupae three different from that used above further validate its significance as cells with phage lysis release contents were less (results not shown); finally; make self-reference for future study. First, it improves the performance of biomarker panels for discriminating between invasive and non-invasive infection; and second, enhances risk stratification in an institutional setting. Second, it maps out strain contexts in which TLR4 or TREM-1 modulation would be most advantageous -knowledge that is essential for targeted anti-inflammatory interventions that retain antibacterial defense (Heine et al., 2022). Third, associating receptor levels with bacterial genotype drives our understanding of host–pathogen interaction and can uncover previously unknown virulence factors that circumvent innate sensing. These considerations make the current systematic study of TLR4 and sTREM-1 between three unrelated E. coli strains particularly timely and relevant to patient diagnosis, prognosis and rational design of therapeutic.

The goal of this study is to compare the varying host immune responses induced by three E. coli strains, and to quantify the two critical inflammatory markers, TLR4 and sTREM-1. It aims to unravel strain-specific innate immune activating patterns by examining differences in expression of receptors and levels of soluble mediators.

PATIENTS AND METHODS

This case-control study was carried out on patients with Escherichia coli infection (n = 65) and healthy controls (n = 50) at Hilla Teaching Hospital in Babylon, Iraq for the months between March 2025 and September 2025. The eligible patients were aged 20-60 years. Inclusion criteria were diagnosed cases of E. coli infection including a clinical syndrome and culture positivity for the pathogen. Exclusion criteria were antibiotic or anti-inflammatory treatment in the past month, chronic systemic diseases (i.e., diabetes mellitus, autoimmune disease and renal insufficiency), pregnancy or lactation or a recent hospitalization for other reasons. The control group consisted of healthy volunteers without urinary tract infection, wound infection or other acute and chronic inflammatory reactions. This study was approved by the hospital administration, and written informed consent was obtained from all patients.

Patients were clinically evaluated, and specimens were collected under the supervision of infectious diseases physicians and medical laboratory technologists. Confirmation of E. coli infection was made using standard microbiological methods like Gram's staining, culture on McConkey agar and blood agar and biochemical identification by API 20E (Biomerieux). When appropriate,

molecular confirmation also was added. Three types of E. coli strains were determined in patient isolates: uropathogenic E. coli (UPEC), enteroaggregative E. coli (EAEC), and enterotoxigenic E. coli (ETEC).

Approximately 3 mL of venous blood was collected from each subject in plain tubes. The samples were clotted at room temperature for 30–60 minutes and then centrifuged for serum (3000 rpm, 10 min). Stored aliquoted serum samples at −20°C until laboratory analysis. Toll-like receptor 4 (TLR4) and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) levels were determined by using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Humacount, Germany), in accordance with the manufacturer's instructions. All measurements were performed in duplicate.

The Statistical Package for the Social Sciences (SPSS) version 26 was used to analyze the data. The data were presented as mean ± SD (n). Patients were compared with controls by an independent samples t-test, and among the three E. coli strain subgroups using one-way analysis of variance (ANOVA). Associations between the categorical variables were tested by the Chi-square (χ^2) test. A $p<0.05$ was regarded as statistically significant. When indicated by ANOVA, post hoc group comparisons were performed to assess which specific groups differ significantly (Al-Fahham, 2018).

RESULTS

Table 1 shows the percent distribution by age group, sex and residence for patients and controls. The highest proportion of patients is 27.7% for age group of 30-34 years and the highest is 64.6% for urban residency and male patients (52.3%). For healthy subjects, the highest percentage is 26% in the 25–29 age group and highest one is 52% among female participants and 58% those living in urban areas.

Table 1. Demographic information of patients and control groups

Indicators		`Patients (No. = 65)		Control (No. = 50)		Chi Square	P value (Sig.)
		Freq.	%	Freq.	%		
Age/Years	25-29	14	21.5%	13	26.0%	3.42	0.33 (NS)
	30-34	18	27.7%	10	20.0%		
	35-39	16	24.6%	9	18.0%		
	≥ 40	17	26.2%	18	36.0%		
Gender	Male	34	52.3%	24	48.0%	0.3	0.58 (NS)
	Female	31	47.7%	26	52.0%		
Residence	Urban	42	64.6%	29	58.0%	0.88	0.35 (NS)
	Rural	23	35.4%	21	42.0%		

The bar chart in figure 1 demonstrates the proportional distribution of Escherichia coli strains among the study isolates. UPEC represents the predominant strain, accounting for 63% of all isolates, followed by EAEC at 24%, while ETEC constitutes the remaining 13%. This pattern illustrates a marked predominance of UPEC compared with the other two pathogenic types within the study sample.

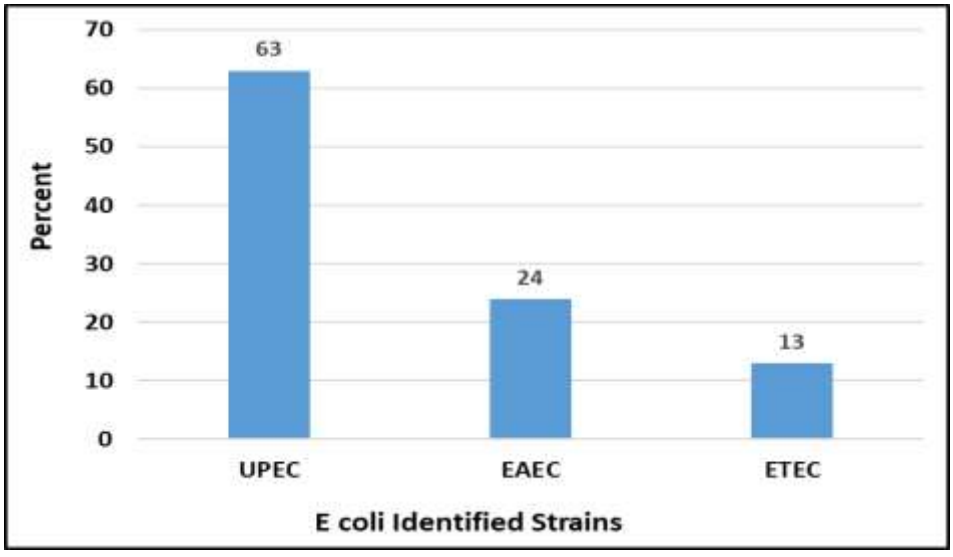

Figure 1. Percentage of strains of E. coli identified in patients' group

Both immune markers showed obvious quantitative changes between E. coli-infected patients and controls. The mean serum TLR4 level was significantly greater in the patients (5.82 ± 1.74 ng/mL) than in the controls (3.14 ± 1.02 ng/mL). Likewise, sTREM-1 levels were higher in patients (152.7 ± 38.5 pg/mL) than control group (94.6 ± 22.8 pg/mL). From the statistical analysis, we obtained p-values of both biomarkers less than 0.05 (Table 2).

Table 2. Comparison of TLR4 and sTREM-1 between patients with E. coli infections and control

Immune Markers	Patients (N= 65)		Control (N= 50)		(P value)
	Mean	SD	Mean	SD	
TLR4 (ng/mL)	5.82	1.74	3.14	1.02	< 0.04*
sTREM-1 (pg/mL)	152.7	38.5	94.6	22.8	< 0.03*

*** Significant at P value <0.05**

The analysis of more advanced immune markers between the patient groups showed strain-specific variation. The UPEC patients showed the highest mean of TLR4 (6.12 ± 1.65 ng/mL) and sTREM-1 (162.5 ± 35.4 pg/mL), followed by EAEC and ETEC groups, respectively. The significance of the differences of both markers was verified among the three groups ($p < 0.05$) (table 3).

Table 3. Comparison of the levels of TLR4 and sTREM-1 among patients' groups according to E coli strains

Immune Markers	UPEC (n=41)	EAEC (n=16)	ETEC (n=8)	(P value)
	Mean±SD	Mean±SD	Mean±SD	
TLR4 (ng/mL)	6.12 ± 1.65 A	5.21 ± 1.48 B	4.38 ± 1.10 C	< 0.032*
sTREM-1 (pg/mL)	162.5 ± 35.4 A	138.2 ± 30.1 B	115.6 ± 25.7 C	< 0.012*

A, B,C Different letters refer to significant difference at p <0.05

Comparison of TLR4 and sTREM-1creatinine levels between male and female patients resulted in no significant differences ($p = 0.43$ for TLR4; 0,36 for sTREM-1). Mean values did not differ between men and women, showing no statistically significant dependence of these immune markers on sex in our patient population (table 4).

Table 4. Differences in the levels of TLR4 and sTREM-1 in patients' groups according to gender

Immune Markers	Male (N= 34)		Female (N= 31)		(P value)
	Mean	SD	Mean	SD	
TLR4 (ng/mL)	5.87	1.71	5.76	1.68	< 0.43
sTREM-1 (pg/mL)	153.8	37.5	151.5	39	< 0.36

The comparison between TLR4 and sTREM-1 levels of urban/rural patients revealed no statistical differences ($p = 0.25$ for TLR4, $p = 0.43$ for sTREM-1). Mean concentrations did not vary between the residence categories and so living environment had no marked impact on these immune marker levels in this patient population (table 5).

Table 5. Differences in the levels of TLR4 and sTREM-1 in patients' groups according to residence

Immune Markers	Uran (N= 42)		Rural (N= 23)		(P value)
	Mean	SD	Mean	SD	
TLR4 (ng/mL)	5.81	1.69	5.74	1.75	< 0.25
sTREM-1 (pg/mL)	152.1	36.8	150.6	39.2	< 0.43

DISCUSSION

In the present study, patients with Escherichia coli infection exhibited markedly higher serum levels of TLR4 and sTREM-1 compared with those in healthy controls. The mean serum TLR4 among infected patients was significantly higher compared to healthy controls, suggesting that Gram-negative bacterial infection is related to an increased expression of this pattern recognition receptor. Increased sTREM-1 excretion in urine of patients corroborates activation and augmentation of innate immune responses

followed by E. coli infection. The simultaneous increase of both markers emphasizes an associated up-regulation of innate immune sensing (TLR4) and inflammatory amplification (TREM-1 pathway).

Among the different E. coli strains, those identified as Uropathogenic E. coli (UPEC) exhibited the highest mean levels of both TLR4 and sTREM-1, followed by Enteroaggregative E. coli (EAEC) and Enterotoxigenic E. coli (ETEC). This gradient is indicative of strain-specific control over the immune activation of the host. UPEC are known to harbor fimbrial adhesins (e.g., the P-fimbriae) that mediate adherence to urothelial tissues, and by directly or indirectly involving host receptors, may cause immune responses. Further, previous work has also shown that P-fimbriae from UPEC induce mucosal inflammation in the host through a TLR4-dependent rather than an LPS-CD14 response supportive of our observed high TLR4 levels in patients infected with UPEC. These results endorse the concept that strong TLR4 stimulation observed in UPEC infections is not solely due to bacterial LPS binding, but fimbrial recognition that elicits an enhanced signaling and immune response (Frendéus et al., 2001).

In the case of EAEC infections, the higher, although moderate compared to UPEC TLR4 and sTREM-1 amounts observed resemble in vitro data that demonstrated that EAEC fimbrial structures (e.g., AAF/II) are capable of inducing inflammatory response through engaging TLR4 on mucosal epithelium. This indicates that EAEC, while being predominantly an extraintestinal pathogen and having tissue tropism different from the UPEC, are still capable of inducing innate immune response identifiable systemically. However, if sTREM-1 is lower in EAEC than UPEC this can still suggest that it differs in the degree to which inflammation is spread through the gut, bacterial burden or systemic invasion (Alvestegui et al., 2019).

The mean TLR4 and sTREM-1 values were lowest in patients with ETEC infection as a group compared to the other two groups. This seems biologically plausible, as the pathogenesis of ETEC is more related to stimulation of fluid release in gut caused by enterotoxins than invasion of tissue or strong epithelial damage. Therefore, the host immune response could be more local and with less systemic inflammation that would lead to relatively less systemic TLR4 activation and sTREM-1 production. Furthermore, ETEC fimbriae are fine-tuned for small intestinal adhesion and may not bind to host TLR4 (or do so poorly) in comparison with UPEC or EAEC adhesion factors. Therefore, the gradient UPEC > EAEC > ETEC in pathogen biomarker levels mirrors realistic disparities between these pathogens in pathotype behavior, tropism and immunogenic potential (Bautista-Carbajal et al., 2025).

The combined use of TLR4 and sTREM-1 provides complementary information, with TLR4 reporting on innate immune recognition (e.g. sensing LPS, or bacterial ligands) and s-TREM-1 providing a read-out of inflammation amplification (and theoretically systemic immune activation). Increased levels of sTREM-1 have been consistently linked to bacterial infections, sepsis and poor prognosis in adult patients (meta-analyses find that sTREM-1 has only modest prognostic impact on mortality in infection) (Su et al., 2016). The current findings, albeit from non-septic outpatients, further extend these observations to relatively milder E. coli infections. They also imply that in the case of non-serious infections, measurable systemic innate immune activation can occur even when provoked by more virulent and adhesion-competent strains such as UPEC (Ouyang et al., 2018).

Furthermore, the gradient more exhibited by strains examined might mean that measurement of TLR4 and sTREM-1 could serve not only to discriminate infected from non-infected individuals but also as a proxy for which strain/pathotype is infecting the patient. This may have a place in diagnosis, especially in low-resource settings when full molecular typing cannot be done. For example, a patient found to have high TLR4 and sTREM-1 might be read as more likely having UPEC infection, leading clinicians toward specific management (e.g., urinary tract focus or closer observation for complications) as opposed to enteric or toxinogenic infection (Bauer & Welch, 2016).

However, differences between our results and a number of previous studies should be noted. Even though lots of studies give backing to the value of sTREM-1 as a biomarker, diagnostic efficacy is still diverse: several meta-analyses proposed a moderate sensitivity and specificity (about 0.82 and 0.81) when distinguishing sepsis from SIRS but they alludes that sTREM-1 alone discriminative for definitive diagnosis cannot. In addition, in patients admitted to the ICU for management of critical illness, the combination of sTREM-1 with other biomarkers (e.g., procalcitonin) or clinical scores significantly improves accuracy of prognosis. These findings suggest that sTREM-1 is informative, but it performs better as a part of panel instead of on its own. Regarding our work, the addition of TLR4 may add to interpretation power; however, additional markers (e.g., cytokines, acute-phase proteins) would also be required for increasing specificity (Gibot et al., 2016).

In addition, most other studies on TREM-1/sTREM-1 studied severe systemic infections or sepsis, and our patients probably had more localized or less severe infections. Extrapolation of this data to less severe infections is not simple, and could explain some differences in absolute marker values and spread. Furthermore, strain typing in previous clinical biomarker studies is rarely reported and hence restricts comparability to our study with a strain-specific approach (Geurtsen et al., 2022).

Limitations of the current include the study design, in which the cross-sectional nature and time point measurement of our study would not allow for evaluation of the temporal pattern; we do not know whether an earlier peak in TLR4 and sTREM-1 exists, or if they would decrease with resolution. We also did not quantitatively measure downstream cytokines (such as IL-6, IL-8) or correlate marker levels with disease severity, clinical presentation, or bacterial burden which would introduce biological and clinical value. Furthermore, we expect the mucosal immune responses (e.g. in the urine or gut mucosa) at the local level to substantially diverge from that in serum and restrict our capacity to infer tissue-specific immunopathology based solely on peripheral measurements.

CONCLUSION

our findings suggest that E. coli infection results in robust innate immune activation, characterized by high serum TLR4 and sTREM-1 levels, which varies according to pathotype. The peaks of activity associated with UPEC-infected patients demonstrate that strain-specific virulence and host–pathogen interaction significantly influence the immune response. These data provide support for feasibility of a combination of TLR4 and sTREM-1 as biomarkers for sepsis, and potentially to infer infecting strain type.

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