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Soluble urokinase plasminogen activator receptor as a biomarker of antibiotic-resistant patterns of Gram-negative bacterial infections: a case-control study

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ABSTRACT

The soluble urokinase plasminogen activator receptor (SuPAR) is an emerging biomarker associated with various clinical disorders; however, its utility in identifying antimicrobial-resistant (AMR) bacterial infections remains underexplored. AMR bacteria pose a significant global health challenge, with certain Gram-negative bacteria exhibiting considerable resistance to multiple antibiotics. This case-control study aimed at evaluating the diagnostic accuracy of SuPAR in detecting severe Gram-negative AMR bacterial infections. A total of 100 samples were analysed, comprising 60 clinically diagnosed cases of Gram-negative bacterial infections and 40 control samples. Pathogens were identified by using conventional laboratory techniques (including Gram staining, culture, colony morphology, and biochemical assays), supplemented by automated methods such as the VITEK2 Compact system for bacterial identification and antimicrobial susceptibility testing. Serum SuPAR levels were quantified *via* an enzyme-linked immunosorbent assay (ELISA). SuPAR levels were found to be significantly elevated in infected patients compared to controls (p=0.0006). Among the resistance profiles, extensively drug-resistant (XDR) infection cases exhibited the highest SuPAR levels, followed by multi-drug resistant (MDR) cases (p=0.0003). Non-MDR infection cases exhibited moderately elevated levels relative to controls. Across pathogen types, *Acinetobacter baumannii* was associated with the highest SuPAR levels, while *Burkholderia cepacia* exhibited the lowest. Notably, elevated SuPAR levels were also observed

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in cases of skin infection and sepsis. In conclusion, SuPAR levels were found to be markedly increased in patients with Gram-negative bacterial infections, particularly in those involving XDR and MDR strains, thereby suggesting its potential role as a biomarker in assessing antimicrobial resistance severity.

1. Introduction

Antimicrobial resistance represents a major global health challenge, with specific bacteria exhibiting resistance to multiple antibiotics[1]. Gram-negative bacteria are among the most concerning pathogens due to their high levels of antibiotic resistance[2]. According to the World Health Organization (WHO), drug-resistant infections currently account for at least 700,000 deaths annually, with projections estimating up to 10 million deaths per year by 2050[1]. *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* are prominent Gram-negative bacteria known for their multidrug resistance[3].

Antibiotic resistance can be categorized into three types: (i) innate resistance (conferred by genes encoding efflux pumps and reduced membrane permeability), (ii) acquired resistance (resulting from chromosomal mutations or horizontal gene transfer *via* transformation, transposition, or conjugation), and (iii) environmentally-induced resistance (occurring *via* genetic or metabolic adaptations)[3]. Resistance profiles are further classified as follows: (i) multidrug-resistant (MDR) bacteria (displaying resistance to at least one agent in three or more antimicrobial groups), (ii) extensively drug-resistant (XDR) bacteria (displaying resistance to all but one or two antimicrobial groups), and (iii) pan-drug-resistant (PDR) bacteria (displaying resistance to all available antibiotics)[4].

While culture-based assays remain the gold standard for assessing antimicrobial resistance in Gram-negative bacilli, results typically require 24–48 h, potentially delaying treatment in critically ill patients. Such delays may exacerbate illness and increase mortality risk. Therefore, rapid diagnostic methods – including those that assess resistance profiles directly from clinical specimens – are increasingly critical[5]. Rapid diagnostic tests are now integrated into many laboratories and emergency departments in order to accelerate diagnosis, enhance infection control, guide initial therapeutic decisions, and support antimicrobial stewardship in high-throughput environments[6]. Additionally, evaluating inflammatory biomarkers may offer indirect, yet timely evidence of bacterial infection and may help optimize antimicrobial therapy in high-risk populations[7].

The soluble urokinase plasminogen activator receptor (SuPAR) is an inflammatory biomarker released after cleavage of its glycosylphosphatidylinositol anchor during innate immune activation. SuPAR is thought to play a chemotactic role in guiding leukocyte migration, and it is expressed in multiple cell types including leukocytes, macrophages, fibroblasts, cardiomyocytes, and renal tubular cells. SuPAR levels can be quantified in plasma by using an enzyme-linked immunosorbent assay (ELISA)[8].

This study has assessed the utility of SuPAR as part of a diagnostic panel for identifying MDR Gram-negative bacterial infections. Our goal was to contribute to the development of more rapid and accurate diagnostic approaches for these difficult-to-treat infections.

2. Methodology

2.1. Patients

We conducted a descriptive case-control study between October and December 2024 across three hospitals: the Al-Husseini Teaching Hospital, the Al-Kafeel Specialized Hospital, and the Imam Hassan

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Table 1. Comparison of the soluble urokinase plasminogen activator receptor (SuPAR) levels (in ng\L) between control and patient groups, as stratified by pathogen type, antimicrobial resistance profile, and infection site. Note: different letters as superscripts after the mean values indicate statistically significant differences between these values. Abbreviations used: MDR, multidrug-resistant; XDR: extensively drug-resistant.

Groups	Subgroup	Mean	SD	*p*-value
Pathogen types	control	59.41 [a]	11.10	0.0006
	Klebsiella pneumonia	126.75 [b,c]	103.16	
	Escherichia coli	174.61 [b,c]	74.63	
	Acinetobacter baumannii	216.27 [c]	81.86	
	Pseudomonas aeruginosa	156.60 [b,c]	72.92	
	Burkholderia cepacia	103.35 [a,b]	6.53	
Antimicrobial resistance profile	XDR	190.98 [c]	94.37	0.0003
	MDR	169.72 [b,c]	76.02	
	non-MDR	128.12 [b]	45.53	
Type of infection	urinary tract infection	151.66 [b,c]	68.61	0.0005
	respiratory tract infection	191.87 [b,c]	101.16	
	sepsis	172.76 [b,c]	106.92	
	skin infection	206.51 [c]	106.92	
	meningitis	123.34 [a,b]	21.74	

Al-Mujtaba Hospital. The study included 60 cases of Gram-negative bacterial infection from various infection sites and 40 healthy controls.

2.2. Inclusion and exclusion criteria

Bacterial infections were clinically diagnosed by attending physicians. Inclusion criteria: clinical suspicion of Gram-negative bacterial infection, elevated white blood cell count and C-reactive protein levels, and site-specific symptoms consistent with infection. Exclusion criteria: age <18 years, diagnosis of an autoimmune disease, pregnancy, history of malignancy, and prostate disorders in male patients.

2.3. Collection of the samples

Samples were collected from infection sites and were inoculated onto blood agar, nutrient agar, and MacConkey agar plates. Blood cultures were processed using brain heart infusion broth. Urine specimens were cultured using semi-quantitative methods. All inoculated plates were incubated aerobically at 37°C for 16–18 h. Gram stains were prepared for provisional identification, followed by subculturing and analysis using the VITEK-2 Compact system for both bacterial identification and antimicrobial susceptibility testing.

2.4. Ethical approval

Ethical approval was obtained from the Ethics Committees of the Kerbela Health Office and from the College of Medicine of the University of Kerbala (approval number: 1259; date: 1 October 2024). Written informed consent was obtained from all participants.

2.5. Statistical analysis

Statistical analyses were performed using the IBM SPSS version 23 software. Mean values and standard deviations were calculated, while significance was determined using *p*-values. Comparisons among multiple groups were conducted using analysis of variance (ANOVA), followed by Duncan's *post hoc* test for pairwise comparisons.

3. Results

The study included 60 infected patients (26 fe-

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males, 43.33%; 34 males, 56.66%) and 40 healthy controls. The infection site distribution was as follows: urinary tract infections (28.33%), respiratory infections (28.33%), sepsis (20%), skin infections (20%), and meningitis (3.33%). As shown in Table 1, the SuPAR levels varied significantly across infection sites and between infected patients and controls (p=0.0005). All infection groups exhibited markedly elevated SuPAR levels compared to controls (59.41 ± 11.10 ng/L). Skin infections had the highest mean SuPAR levels (206.51 ± 106.92 ng/L), followed by respiratory tract infections (191.87 ± 101.16 ng/L), sepsis (172.76 ± 106.92 ng/L), urinary tract infections (151.66 ± 68.61 ng/L), and meningitis (123.34 ± 21.74 ng/L). As seen in Table 1, significant differences were also observed across different antimicrobial resistance profiles (p=0.0003), and across different pathogens (p=0.0006).

4. Discussion

This study yielded three main findings. Firstly, SuPAR levels at admission varied significantly by infection site, with the highest levels observed in skin infections and the lowest in meningitis. Secondly, SuPAR levels were found to be significantly higher in cases of a resistant infection, peaking in XDR cases, followed by MDR and then non-MDR bacterial infections, thereby, suggesting a relationship between SuPAR levels and the severity of antimicrobial resistance. Finally, among the identified infections, those caused by *Acinetobacter baumannii* were associated with the highest SuPAR levels, potentially reflecting infection severity.

Our results echo earlier findings demonstrating elevated SuPAR in MDR infections (mean: 15.4 ng/L *vs.* 8.2 ng/L in susceptible strains)[9]. They also align with reports identifying *K. pneumoniae* as having the highest proportion of XDR isolates, followed by *P. aeruginosa* and *E. coli*[4]. However, our data differ from those of *in vitro* studies suggesting a strong presence of XDR *P. aeruginosa*[10].

One should note that this study was retrospective, with SuPAR levels measured only at hospital admission, and involving a relatively small sample size. Future research should consider multicenter, prospective designs with larger cohorts and serial SuPAR measurements in order to validate these findings.

5. Conclusion

We strongly advocate for the use of novel biomarkers (such as SuPAR) in order to aid clinicians in assessing the severity of bacterial infections and guiding appropriate antibiotic therapy. A panel-based biomarker approach can deliver valuable diagnostic insights in high-risk populations, support antimicrobial stewardship, and reduce inappropriate antibiotic use.

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Conflicts of interest

None exist.

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