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Evaluation of serum IL-36 γ as a potential discriminatory biomarker for *Acinetobacter baumannii* infection

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ABSTRACT

Interleukin-36 γ (IL-36 γ) is one of the IL-1 family cytokines and plays a role in innate immune and inflammatory responses against bacterial infection. Objective: to assess serum IL-36 γ level and its potential discriminative value in patients with *Acinetobacter baumannii* infection. A case-control study in 82 patients with aster confirmed *A. baumannii* infection and 98 asterisk apparently healthy control subjects was conducted in Al-Hilla Teaching Hospital, the capital of Babylon Governorate, Iraq, during the period from April until to July 2026. Concentrations of serum IL-36 γ were determined by enzyme-linked immunosorbent assay (ELISA). Patients with *A. baumannii* infection had a higher mean serum IL-36 γ concentration than healthy controls (42.8 ± 15.6 pg/mL vs 27.4 ± 9.8 pg/mL, $p < 0.001$). Receiver operating characteristic (ROC) curve analysis indicated that IL-36 γ has a high discriminatory performance, yielding an AUC of 0.86. For IL-36 γ , the sensitivity and specificity at a cutoff value of 34.5 pg/mL were 82.9% and 79.6%, respectively. Our results suggest that serum IL-36 γ is markedly higher in *A. baumannii* infected patients and might represent a discriminative biomarker between the infected patients and the healthy controls. Validation of the discriminatory utility of IL-36 γ in larger populations and more clinically relevant comparison groups is needed.

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Introduction

It is increasingly accepted that *Acinetobacter baumannii* acts as an important opportunistic pathogen and is one of the most prevalent healthcare-associated pathogens, especially in critically ill and hospitalized patients (Howard et al., 2012). The organism is highly linked with ventilator-associated pneumonia, bloodstream infections, wound infections, urinary tract infections, and infections associated with invasive medical devices. *A. baumannii* can persist in the hospital environment (Kubin et al., 2024), colonize susceptible patients (Yehya et al., 2024), form biofilms, and acquire multiple antimicrobial-resistance mechanisms, which have rendered it

increasingly difficult to treat clinically (Kubin et al., 2025; Yehya et al., 2025). The most worrisome is that of carbapenem-resistant *A. baumannii* (CRAB) that continues to fall in the highest-priority bacteria groups as treatment options continue to dwindle. Recent studies have reiterated that *A. baumannii* infections are a significant cause of morbidity and mortality, especially in critical-care populations (Richards et al., 2024; Kubin et al., 2025).

Furthermore, the clinical diagnosis *A. baumannii* infection is further complicated by the ability of the organism to colonize hospitalized patients without causing invasive disease (Russo & Serapide, 2025). It is especially critical in respiratory specimens where isolation of *A. baumannii* can be the result of either colonization, or actual clinically important infection. Therefore, microbiological isolation alone may not be a sufficient reflection of the presence and/or severity of infection. In a recent study that evaluated patients with pulmonary *A. baumannii* colonization or infection, conventional inflammatory markers such as procalcitonin and neutrophil counts have utility in providing some discriminatory information, thus highlighting the need for objective biomarkers that can differentiate between infection and colonization (Utility of sTREM-1 Biomarker and hep Gene (Feng et al., 2022).

The host response to *A. baumannii* is typified by the activation of innate immune-recognition pathways that trigger the production of pro-inflammatory cytokines and chemokines (Chen, 2020). The bacterial components such as lipooligosaccharide or outer-membrane proteins are capable of triggering pattern recognition receptors, including Toll-like receptor 2 and Toll-like receptor 4, which activate nuclear factor- κ B and mitogen-activated protein kinase signaling cascades. These processes induce the mediation of which interleukin (IL)-1 β , IL-6, IL-8, tumor necrosis factor- α and other chemokines are recruited for neutrophil and macrophage infiltration (Mortensen et al., 2012; Tiku et al., 2022). Most relevant to this review, more recent work reinforces the notion that the host response is a key driver of the outcome of *A. baumannii* infection, although the amplitude and composition of the host immune response may be determined in a strain- and model-dependent manner as well in terms of host characteristics and disease severity (Sabatini et al., 2024).

IL-36 cytokine family has gained interest in this context, due to its positioning at the junction of epithelial tissues and innate immunity in this larger inflammatory network. IL-36 γ , one of the three main IL-36 agonists, is a member of the IL-1 cytokine superfamily with a unique expression profile predominantly produced by epithelial cells and certain myeloid cell populations (Satoh et al., 2026). Upon appropriate activation and subsequent proteolytic processing, IL-36 γ interacts with the IL-36 receptor and stimulates downstream inflammatory signaling via NF- κ B and mitogen-activated protein kinase (MAPK) pathways. IL-36 γ can act through these mechanisms to modulate antimicrobial responses, inflammatory-cell recruitment, and cytokine production (Sugiura, 2024).

Studies performed with bacterial infection models indicate that IL-36 γ is involved in conferring protective host defense, especially at mucosal sites. In a model of experimental bacterial pneumonia, IL-36 γ deficiency was associated with impaired bacterial clearance and dissemination, and mortality after infection with *Streptococcus pneumoniae*, while protective effects were similar in a *Klebsiella pneumoniae* pneumonia model (Kovach et al., 2017). IL-36 γ has been linked to enhancing macrophage antimicrobial functions in tuberculosis through mechanisms dependent on autophagy and WNT5A signaling pathway (Gao et al., 2019). Crucially, novel clinical and experimental evidence has showed elevated expression of IL-36 γ in pulmonary pathological tissue, peripheral blood mononuclear cells and serum in active pulmonary tuberculosis, as well as serum IL-36 γ being potentially diagnostic. This result supports that circulating IL-36 γ indicates immune activation as an artifact from infection, not simply local tissue inflammation (Gao et al., 2026).

While knowledge is beginning to accumulate regarding the role of IL-36 γ in bacterial host defense, its involvement and mechanism of action for *A. baumannii* infection remains incompletely defined and particularly for human clinical populations. Recent mucosal immunity studies of *A. baumannii* have mainly focused on the established inflammatory mediators (i.e. IL-6, IL-8, TNF- α , IL-1 β , IL-17) whereas the diagnostic potential of newer cytokines has been given far less attention (Garlanda et al., 2025). Hence, the present study was performed to assess serum concentrations of IL-36 γ in *A. baumannii*-infected patients and whether this cytokine could serve as a prognostic biomarker to discriminate infection.

Patients and Methods

Study Design and Setting

This was a case–control study performed from April to July 2026 at A-Hilla Teaching Hospital in Babylon City, Iraq. This study to determine serum concentrations of interleukin-36 gamma (IL-36 γ) in patients with *Acinetobacter baumannii* infection as compared to seemingly healthy individuals. Al-Hilla Teaching Hospital is one of the largest health care facilities in the Babylon Governorate and attracts patients from Hilla and other nearby areas becoming a suitable clinical site for the enrollment of patients having bacterial infections.

Study Population

This analysis was conducted on 180 participants; 82 patients with positive *A. baumannii* infection who comprise the case group and 98 apparently healthy individuals that act as a control group. Consecutive enrolment of patients using pre-defined inclusion and exclusion criteria. The patients were defined as clinical cases of *A. baumannii* infection with evidence for the isolation of this pathogen from an appropriate clinical specimen. Patients were eligible if microbiological findings were deemed by the attending physician to be consistent with clinical and/or working diagnosis. Control group consisted of apparently healthy individuals who had no any current clinical evidence of acute infection and had history of *A. baumannii* infection prior to enrollment. Exposure to systemic immunosuppressive therapy during the weeks before screening, investigator-documented acute infectious diseases other than the investigational infection, known chronic inflammatory or autoimmune disease, and administration of antimicrobial therapy prior to specimen collection when such therapy would be expected to markedly influence microbiological activity or inflammatory biomarker concentrations were exclusion criteria. Important conditions that were previously known to affect systemic cytokine responses and were identified on clinical assessment were also exclusion criteria.

Clinical and Laboratory Examination

In-person clinical evaluation by trained medical personnel was performed in all participants. Demographic and clinical data was also recorded, including age, sex, medical history, presenting symptoms, and clinical diagnosis for the patients. Clinical specimens were collected based on the suspected site of infection using standard aseptic techniques. Sputum specimens were obtained in sterile, wide-mouth containers before the administration of antimicrobial therapy whenever possible, for patients with suspected respiratory infection. The specimens were first submitted to Gram staining and then cultured on relevant bacteriological media which include blood agar and MacConkey agar. At 35–37°C, plates were incubated in conditions suitable for aerobic growth for 18–24 hours. All Colonies were identified further for *Acinetobacter* species specific morphological properties.

Isolation and Identification of *Acinetobacter baumannii*

Colony morphology, Gram stain, oxidase reaction, and routine biochemical features were used to analyze presumptive isolates of *A. baumannii*. Bacterial identification was finally performed using the VITEK® 2 automated identification system (bioMérieux, France), using specific Gram-negative identification card. The

VITEK 2 system has been widely applied for the identification of clinically significant non-fermenting Gram-negative bacilli, including *A. baumannii*. Identification was also supplemented with molecular detection of the blaOXA-51-like gene (a molecular marker commonly used in conjunction with identification of the *A. baumannii* complex) where available. This is important because phenotypic identification of species within the *Acinetobacter baumannii* complex is often problematic.

Blood Sample Collection and Serum Preparation

Approximately 5 mL peripheral venous blood was aseptically obtained from each participant using sterile disposable blood-collection equipment and plain serum-separator tubes. A clot was allowed to form at room temperature in blood samples before centrifugation at ~3,000rpm for 10 minutes. The isolated serum was then gently pipetted into sterile, labelled Eppendorf tubes using disposable micropipette tips to prevent contamination. Serum aliquots were stored until analysis at -20°C. Using a technique that might compromise cytokine stability when measuring samples of cytokine, our approach was to thaw samples only once prior to performing the ELISA.

Measurement of Cytokine Levels

Serum IL-36γ concentrations were quantified using a human IL-36γ ELISA Kit (Catalog No. EHIL36G, Thermo Fisher Scientific/Invitrogen, USA). The kit is a solid-phase sandwich ELISA used for the quantitative measurement of human IL-36γ in serum, plasma and cell-culture supernatants. Running on a 96-test format, the manufacturer advises using the spectrophotometric measurement at 450 nm, with 620 nm, available as a reference wavelength. In brief, standards and serum samples were added to wells coated with IL-36γ antibody. Wells were washed to remove unbound material, followed by the addition of the biotin-conjugated detection reagent, and incubated again. Subsequently, streptavidin-horseradish peroxidase and the chromogenic tetramethylbenzidine (TMB) substrate were applied. The enzymatic reaction was stopped using the provided stop solution, and the absorbance was measured at 450 nm using a microplate reader based on the standard curve (Beckman-DU640B, USA). Serum concentrations were expressed in pg/mL, and were calculated from the associated standard curve generated from IL-36γ supplied standards. All samples and standards were analyzed following manufacturer instructions. Samples were analyzed preferably in duplicate, and blank and quality-control wells were incorporated in each assay run for improved analytical reliability and reproducibility.

Ethical Considerations

Before data collection, the study protocol was reviewed and approved by the appropriate institutional ethics committee and the relevant health authorities. Prior enrollment, written informed consent was obtained from all participants. Participants were debriefed on the objective and procedures of the study, and participation was voluntary. Personal information and laboratory results were coded and kept confidential in this study. The research was carried out with the ethical standards of the Committee on Human Experimentation.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 26.0 (IBM Corp., Armonk, NY, USA; <https://www.ibm.com/analytics/spss-statistics-software>) For normally distributed data, continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were summarized as frequencies and percentages. Distribution of continuous variables was evaluated prior to statistical test selection. Student independent-samples t-test was used to compare serum IL-36γ concentrations in patients with infection by *A. baumannii* vs. healthy controls. For categorical variables such as sex and other demographic characteristics, the chi-square (χ^2) test or Fisher's exact test (when appropriate) was used for comparison. We then evaluated the discriminatory performance of serum IL-36γ for identifying *A.*

baumannii infection using receiver operating characteristic (ROC) curve analysis. Receiver operating characteristic (ROC) curve was generated and area under the curve (AUC), optimal cut-off value, sensitivity, specificity, positive and negative predictive value were calculated wherever applicable. Statistical significance is defined as a two-sided p -value < 0.05 .

Results

In the demographic distribution of the study participants, there were no statistically significant differences ($P > 0.05$) between the *A. baumannii* infection group and the healthy control group with respect to age, sex or residence (Table 1). The largest age category among patients was those aged >44 years (47.6%) and among controls it was 35–44 years (31.6%); nevertheless, there was no statistically significant difference in age distribution between groups ($\chi^2 = 0.84$, $P = 0.66$). There was no significant difference in sex distribution ($\chi^2 = 0.06$, $P = 0.81$), with males comprising 62.2% of patients and 65.3% of controls. A comparable proportion of patients (59.8%) and controls (59.2%) resided in urban areas, and the difference according to residence was not statistically significant ($\chi^2 = 0.01$, $P = 0.94$).

Table 1. Distribution of age, sex and residence among study subjects

Indicators		Patients (No. = 82)		Control (No. = 98)		Chi Square	P value (Sig.)
		Freq.	%	Freq.	%		
Age/Years	25-24	20	24.4	29.00	29.6	0.84	0.66 (NS)
	35-44	23	28	31.00	31.6		
	> 44	39	47.6	38	38.8		
Sex	Male	51	62.2	64	65.3	0.06	0.76 (NS)
	Female	31	37.8	34	34.7		
Residence	Urban	49	59.8	58	59.2	0.01	0.11 (NS)
	Rural	33	40.2	40	40.8		

NS: Non-significant at $P > 0.05$

Patients with *A. baumannii* infection similarly showed a markedly increased serum concentration of IL-36 γ compared with healthy controls ($P < 0.001$ for each). Patients harbor higher levels of serum IL-36 γ . The average serum IL-36 γ level was 42.8 ± 15.6 pg/mL in patients and 27.4 ± 9.8 pg/mL in controls. This difference was statistically significant ($t = 8.19$, $P < 0.001$), suggesting that increased systemic IL-36 γ responses occur in *A. baumannii* infection patients compared with controls.

Table 2. Differences in IL-36 γ levels between patients with *Acinetobacter baumannii* and control participants

HS:	Groups	Patient (n= 82)	Control (n=98)	T Test	(P Value)
	IL-36 γ (pg/mL)	42.8 $\pm$ 15.6	27.4 $\pm$ 9.8	8.19	P < 0.01
	Mean $\pm$ SD				(HS)

Significant at P<0.05

Since IL-36 γ is a proinflammatory and locally acting member of the IL-1 cytokine superfamily assisting epithelial and innate immune responses, the elevated concentrations of IL-36 γ in infected patients appear biologically plausible. Its expression at mucosal surfaces is particularly salient, since it can participate in a bidirectional dialogue between epithelial cells and immune cells upon microbial assault. Indeed, experimental evidence has shown bacterial infection drives IL-36 γ production in the respiratory tract (Huang et al., 2019), suggesting that our observation of increased serum concentration may indicate activation of host innate immune pathways during infection. In their study, Kovach et al. (2017) showed pronounced induction of IL-36 γ during experimental bacterial infection and also detected enhanced IL-36 γ levels in pulmonary compartments and plasma of patients suffering from pneumonia-related acute respiratory distress syndrome (ARDS). Their results revealed a novel link between pulmonary bacterial infection and IL-36 γ activation. The current finding of markedly increased serum IL-36 γ in patients with *Acinetobacter baumannii* infection is in line with previous studies suggesting that IL-36 γ is activated after Gram-negative bacterial pulmonary infection. Aoyagi et al. (2017) showed that bacterial infection significantly upregulated the expression of IL-36 γ in pulmonary macrophages and alveolar epithelial cells, and also reported that patients with acute respiratory distress syndrome had markedly elevated IL-36 γ concentrations in plasma and bronchoalveolar lavage fluid in comparison with healthy individuals. In addition, they have been able to experimentally establish an association with IL-36 γ signaling was linked to inflammatory responses and lung injury induced by bacteria infection. These findings support the suggestion that the increased IL-36 γ seen in the current *A. baumannii*-infected cohort reflects activation of the host inflammatory response to Gram-negative bacterial infection. However, because Aoyagi et al. studies into *P. aeruginosa*, but not *A. baumannii*, and whose patients presented with acute respiratory distress syndrome, the current data should be viewed as evidence extending the role of IL-36 γ in Gram-negative bacterial infection as opposed to a pathogen-specific response (Aoyagi et al., 2017).

Current results further parallel the experimental finding in Gram-negative respiratory pathogens. Kovach et al. (2017), found that *Klebsiella pneumoniae* infection led to pulmonary IL-36 γ expression, and IL-36 γ deficiency resulted in a defect in bacterial clearance and heightened dissemination. Taken together these findings indicate that IL-36 γ is involved in a local protective response to more than one bacterial species, and is not specific to the response to Gram-positive organisms. Now, the finding that levels of IL-36 γ is elevated in *A. baumannii* infection patients thereby extends the generalized notion of IL-36 γ -mediated responses to a second clinically relevant Gram-negative pathogen. However, previous studies were performed in animal models and with other bacterial species, but not in natural human *A. baumannii* infections to show that IL-36 γ is elevated in *A. baumannii* infection patients (Cavallo et al., 2023).

This observed upregulation, however, could be attributed to the capacity of IL-36 γ to enhance innate immunity signaling when bacteria infect the host. IL-36 γ may bind the IL-36 receptor and activates downstream

signaling pathways such as nuclear factor- κ B and the mitogen-activated protein kinase signaling (Winkle et al., 2026). In experimental pneumococcal pneumonia, IL-36 γ enhanced classical macrophage activation and type-1 cytokine responses, both mechanisms that support antimicrobial immunity (Kovach et al., 2021). Therefore, the increased serum concentration observed in the current patients may be a component of a global host response to bacterial challenge, and thus may not be uniquely *A. baumannii*-specific. This is a particular distinction that can be made when thinking of IL-36 γ as a diagnostic biomarker (Pires & Parker, 2019).

However, earlier studies have demonstrated that the biological effects of IL-36 γ may vary based on the type of pathogen responsible for the infection as well as the inflammatory context. Aoyagi et al. Pulmonary infection with cytotoxic *Pseudomonas aeruginosa* up-regulated IL-36 γ expression in pulmonary macrophages and alveolar epithelial cells (Kobayashi et al. (2017)). In that model, the authors attributed an increase in prostaglandin E2 production and a reduction in bacterial clearance and lung injury to IL-36 γ signaling. Thus, in the future, IL-36 γ should be considered not just as a universally protective cytokine. Instead, its effects likely depend on pathogen features, the tissue environment, the rate of disease progression, and effectively capture the balance between protective antimicrobial responses and tissue-damaging inflammation (Buhl & Wenzel, 2019 ; Peñaloza et al., 2021a).

Evidence of a context-dependent role is also evidenced in work from Peñaloza et al. (2021b) that IL-36 γ was involved in neutrophilic inflammation in the *P. aeruginosa* pulmonary infection model. They report that IL-36 γ action may be substantially dictated by its extracellular proteolytic processing and the inflammatory microenvironment. As a result, the increased levels of serum IL-36 γ observed in this study should mainly be interpreted as evidence of an activated host inflammatory response type related to *A. baumannii* infection, rather than as proof that IL-36 γ itself mediated tissue injury or dictated clinical outcome.

ROC curve analysis showed that serum IL-36 γ performed well in distinguishing patients with *A. baumannii* infection from HC (the area under curve (AUC) is 0.86, $P < 0.001$). IL-36 γ had a sensitivity of 82.9% and a specificity of 79.6% at the estimated optimal cut-off value of 34.5 pg/mL.

Table 4. Receiver operating characteristic (ROC) analysis of IL-36 γ for the diagnosis of *Acinetobacter baumannii*

Biomarker	(AUC)	p-value	Cut-off Point	Sensitivity (%)	Specificity (%)
IL-36 γ	0.86	<0.001	34.5	82.9	79.6

AUC: Area Under the curve

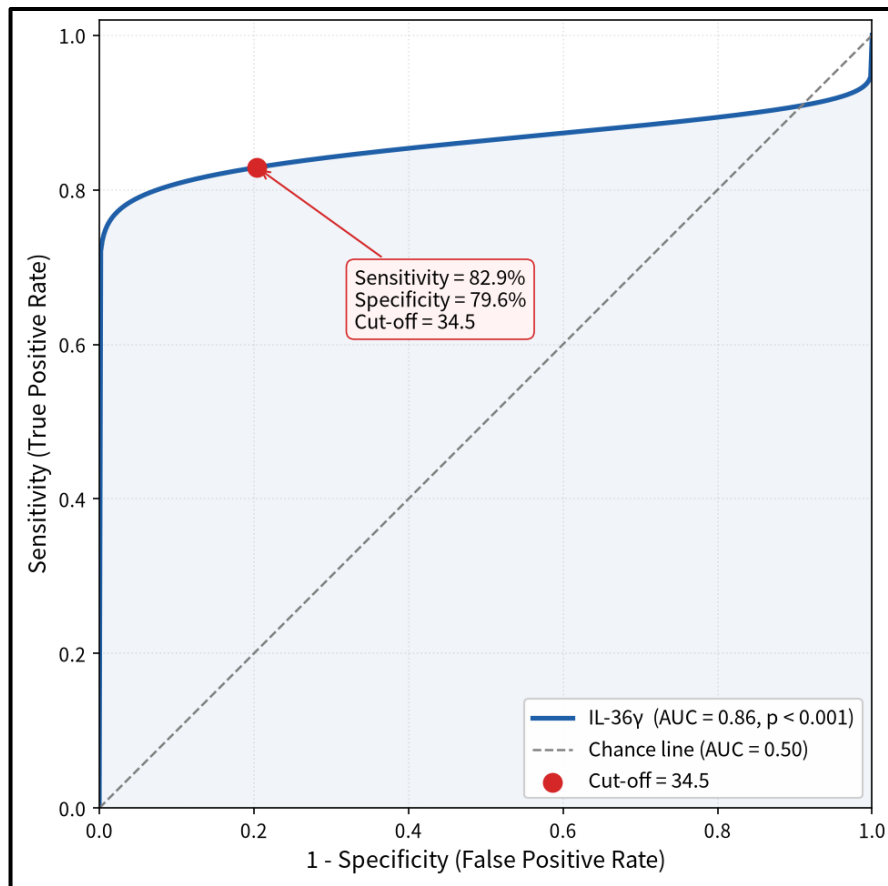


Figure 3. ROC Curve of Serum IL-36 γ Levels for diagnosing *Acinetobacter baumannii*

The ROC performance of IL-36 γ was also one of the important findings of present study. The AUC of 0.86 demonstrates a good discrimination between infected patients and healthy controls in the studied population. The cutoff selected was associated with a sensitivity of 82.9%, implying that many infected patients would be detected, as well as a specificity of 79.6%, indicating that the majority of healthy participants would be classified negative appropriately. These results offer the first evidence that IL-36 γ could serve as a diagnostic tool. However, the term “discriminatory biomarker” must be used with hesitancy since the control group included healthy individuals rather than patients with other bacterial infections or noninfectious inflammatory respiratory diseases. While a biomarker that distinguishes infection from health, has the potential to under-perform when face with clinically indistinguishable diseases (Macleod et al., 2020).

For example, this constraint notably pertains to *A. baumannii* which can colonize the respiratory tract, notably in the context of a hospital stay, particularly in critically ill patients. Therefore, further research should investigate IL-36 γ levels in more representative cohorts including patients with confirmed *A. baumannii* infection, *A. baumannii* colonization, other bacterial pneumonias and non-infectious respiratory diseases. Similar comparisons would demonstrate whether the observed increase is pathogen associated or merely a broad-based inflammatory response. Longitudinal studies in MHC class II deficient ICOS^{-/-} mice could also examine whether IL-36 γ concentration is influenced by disease progression or antimicrobial treatment (Serretiello et al., 2025).

Conclusion:

Both patient and mouse data demonstrate that serum IL-36 γ level is elevated in patients with *Acinetobacter baumannii* infection suggesting an association between this interleukin and the host inflammatory response to infection. The areas under the curve (AUC) were 0.86 by ROC analysis, and the cutoff value was at 34.5 pg/mL with a sensitivity of 82.9% and specificity of 79.6%. The finding indicates that serum IL-36 γ maybe be able to act as a potential discriminatory biomarker in distinguishing *A. baumannii* infection from *A. baumannii* infection. Nevertheless, its diagnostic value must be taken with caution because this study compared infected patients to healthy controls. Larger population studies are warranted as well as patients with other bacterial infectious states and noninfectious inflammatory conditions to further validate our findings.

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