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Adipokine Profiles in Bacteremia: Disease Severity Correlations and Combined Biomarker Analysis

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ABSTRACT

Background: Adipokines, secreted from adipose tissues, play crucial roles in immune and metabolic processes. Their role in severe bacterial infections, such as *Staphylococcus aureus* bacteremia (SAB), remains poorly understood.

Objective: To investigate adipokine serum levels during and after bacteremia and their association with disease severity and clinical outcomes.

Methods: Fifty-two patients with bacteremia (71% *S. aureus*, 29% other pathogens) were matched 1:1 in a prospective case-control study with infection-free controls by age, sex, and comorbidities. Serum levels of adiponectin, resistin, and visfatin were measured during bacteremia, during convalescence, and in controls using ELISA. Disease severity was assessed using Simplified Acute Physiology Score II (SAPS II) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, and adipokine serum levels were correlated with disease severity and hospital mortality.

Results: Resistin (median 25.6 ng/mL vs. 13.8 ng/mL, $p < 0.001$) and visfatin (median 19.3 ng/mL vs. 10.3 ng/mL, $p = 0.004$) were significantly elevated in patients with bacteremia compared to controls. Adiponectin during bacteremia was similar to that in controls, but significantly lower than during convalescence (median 3.5 µg/mL vs. 5.4 µg/mL, $p < 0.001$). *S. aureus* bacteremia showed a trend towards lower adiponectin levels compared to other pathogens. A combined adipokine score using partial least squares (PLS) regression demonstrated superior correlation with disease severity (SAPS II; $\rho = 0.430$, $p = 0.001$) compared to individual adipokines. Exploratory logistic regression showed that including adipokines in a model based on clinical variables may improve mortality prediction (area under the receiver operating characteristic curve [AUC] increase from 0.784 to 0.944).

Conclusions: Adipokines show distinct patterns during bacteremia, with higher levels of proinflammatory resistin and visfatin in bacteremia and higher levels of anti-inflammatory adiponectin in convalescence. While individual adipokines have modest prognostic value, combined scores are associated with disease severity and mortality in severe infections.

1 | Introduction

The pathophysiology of severe bacterial infections involves complex interactions between pathogen virulence factors and host immune responses, including dysregulation of metabolic and

inflammatory pathways [1]. Given the high mortality associated with infections such as *Staphylococcus aureus* bacteremia (SAB), despite advances in therapy [2, 3], a better understanding of these fundamental processes is urgently needed.

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Adipose tissue is recognized as an active endocrine organ secreting numerous cytokines termed adipokines [4]. These molecules serve as crucial mediators between metabolic and immune systems, influencing processes ranging from insulin sensitivity to inflammatory responses [5, 6]. Recent reviews have highlighted the alteration of specific adipokines in critical illness and sepsis, as well as their association with disease severity and outcomes, making them also potential targets for biomarker research [7, 8]. The three major adipokines, adiponectin, resistin, and visfatin, exhibit distinct pro- and anti-inflammatory properties, making them particularly relevant for severe infections.

Adiponectin, the most abundant adipokine, generally exerts anti-inflammatory effects by inhibiting the production of proinflammatory cytokines and enhancing macrophage function [9]. Studies have demonstrated that adiponectin can neutralize lipopolysaccharide activity and may serve as an endogenous protective factor in sepsis [10]. Adiponectin secretion, however, is reduced in adipocytes after staphylococcal infection in vitro [11], and systemic adiponectin levels are reduced during acute illness (reviewed in [12]). In contrast, resistin and visfatin are primarily proinflammatory adipokines. Resistin, originally identified as linking obesity to diabetes [13], is also an acute-phase reactant clustering in an inflammatory cytokine network during sepsis [14]. Visfatin, also known as pre-B cell colony-enhancing factor (PBEF), activates immune cells and induces cytokine production while exhibiting proinflammatory and immunomodulating properties [15]. Clinical studies have linked visfatin serum concentrations to disease severity and organ failure in critically ill patients [16].

Notably, the relationship between adipokines and bacterial infections extends beyond mere biomarker potential. We demonstrated previously that *S. aureus* can survive intracellularly within adipocytes in vitro, altering their cytokine secretion profile and creating a proinflammatory phenotype [11]. Adipocytes also express the functional pattern recognition receptors TLR-1/2 and TLR-2/6 (that recognize gram-positive bacteria) as well as TLR-4 (that recognize lipopolysaccharides from gram-negative bacteria) [17, 18]. Direct recognition of bacteria such as *S. aureus* by adipocytes could thus regulate adipokine secretion. Additionally, adipocytes produce cathelicidin, an antimicrobial peptide, protecting against staphylococcal skin infections [19]. This suggests that adipose tissue not only serves as an energy reservoir and as a source of inflammatory mediators but also as a defense mechanism against invasive skin infections and a potential reservoir for bacterial persistence.

Since adipokines integrate both metabolic and inflammatory information, they hold the potential to be important diagnostic and prognostic biomarkers through their unique dual functionality [8]. The present study aimed to characterize adipokine profiles during and after bacteremia, with a focus on SAB, and to evaluate their potential as biomarkers for disease severity and clinical outcomes using a comprehensive approach including both single- and combined biomarker scoring.

2 | Materials and Methods

2.1 | Study Design and Participants

This prospective matched case-control study was conducted at the University Hospital Regensburg, Germany, between March

2011 and June 2014. The study was approved by the institutional ethics committee (Reference 11-101-0005), and all participants provided written informed consent.

2.1.1 | Cases

Adult patients (≥ 18 years) with bacteremia confirmed by at least one blood culture positive for a clinically relevant pathogen (71.2% *S. aureus* including 2 MRSA isolates, 28.8% other pathogens including *Enterobacteriaceae* [$n = 5$], coagulase-negative staphylococci deemed clinically relevant [$n = 6$], streptococci, and *Pseudomonas* [$n = 2$ each]) and clinical/laboratory signs of infection were enrolled. Blood samples were collected at a median of 3 days (range 0–9 days; IQR [2–4]) after the first positive blood culture (t_0). Convalescence samples were collected after resolution of infection (t_1), median 33 days [range 4–163 days] after [t_0].

2.1.2 | Controls

Infection-free patients admitted for noninfectious reasons were matched 1:1 with cases by age (± 10 years), sex, and important comorbidities (with a focus on metabolic comorbidities such as diabetes mellitus and obesity). In practice, the closest matching candidate from the same ward or department was chosen. Controls had no clinical signs of infection.

2.2 | Data Collection and Clinical Scores

Clinical data included demographics, comorbidities (and the corresponding Charlson Comorbidity Index [20]), laboratory values, and outcomes (mortality, length of stay, and ICU admission). Blood samples were collected during acute bacteremia (t_0) and after clinical improvement (“convalescence”) (t_1) in cases and once in controls (t_0). Disease severity was assessed using the two validated scoring systems APACHE II (Acute Physiology and Chronic Health Evaluation II [21]) and SAPS II (Simplified Acute Physiology Score II [22]).

2.3 | Laboratory Methods

Serum adipokine concentrations were measured in serum samples using commercial ELISA kits following manufacturer protocols, with all samples analyzed in duplicate. Adiponectin and resistin were measured using DuoSet ELISA (R&D Systems, Bio-Techne, Minneapolis, USA), visfatin was measured using a Visfatin ELISA Kit (Uscn Life Science, Gentaur GmbH, Aachen, Germany), and IL-6 using ELISA MAX (BioLegend, Amsterdam, NL). Leukocytes and C-reactive protein (CRP) levels were assessed in serum samples of patients and matched controls at the Institute of Clinical Chemistry and Laboratory Medicine, University Hospital Regensburg, Germany.

2.4 | Outcomes

Primary outcomes included (1) differences in adipokine levels between bacteremia (t_0) and convalescence (t_1) (longitudinal analysis) and in bacteremia (t_0) as compared to controls (t_0) (cross-sectional analysis) and (2) correlation between adipokine levels during bacteremia (t_0) and disease severity scores. Secondary outcomes included pathogen-specific differences in adipokine serum

levels and the correlation of adipokine levels with hospital mortality.

2.5 | Statistical Analysis

Data were analyzed using SPSS (versions 20–25) and R version 4.5. Continuous variables were tested for normality using the Shapiro–Wilk test. Nonparametric tests (Mann–Whitney *U* and Wilcoxon signed-rank) were used for continuous variables, and Pearson’s chi-squared test for categorical data. Spearman’s rank correlation coefficient was used to assess the associations between variables. Bonferroni correction was applied for multiple testing. Statistical significance was set at $p < 0.05$.

A combined adipokine score was derived using partial least squares (PLS) regression to optimize correlation with disease severity (SAPS II scores). PLS was chosen over other approaches such as principal component analysis as it is outcome-guided. Prior to PLS analysis, visfatin and resistin concentrations were log-transformed to improve normality, while adiponectin was retained on its original scale. All adipokine variables were then standardized (z-score transformation: sample mean subtracted and divided by sample standard deviation), ensuring that each variable contributed equally to the analysis regardless of original measurement units or scales. PLS regression was applied with the three standardized adipokines as predictors and SAPS II as the outcome variable. The first PLS component—the single-weighted linear combination most strongly associated with SAPS II—was used as the combined score. The resulting weights reflect each adipokine’s direction and relative contribution to disease severity: a negative weight indicates an inverse association with SAPS

II, and positive weights indicate direct associations. Standardization parameters (means and standard deviations) were derived from the bacteremia group and are reported in the “Results” section to allow score replication.

Nested logistic regression models were developed to predict in-hospital mortality in bacteremia patients. The “base” model included clinical variables: age, sex, body mass index, and CRP concentration. The “full” model additionally incorporated the adipokines as separate predictors (adiponectin on the original scale and log-transformed visfatin and resistin). Model performance was assessed using the area under the receiver operating characteristic curve (AUC). Nested models were compared using likelihood ratio tests following the chi-square distribution. Model parsimony was evaluated using the Akaike information criterion (AIC), with lower values indicating better fit. All analyses were performed on complete cases with no missing values for the specified variables.

Anthropic’s Claude (models Sonnet 3.5 and 4.0) was used to assist in R scripting and to improve the language of the manuscript. All authors reviewed and edited the final content and take full responsibility for the content of the publication.

3 | Results

3.1 | Study Population

A total of $N = 52$ bacteremia patients were matched with $n = 52$ controls. The patient characteristics at baseline (t_0) are summarized in Table 1. Thirty-seven patients (71.2%) had *S. aureus* bacteremia, and 15 (28.8%) had other bacterial pathogens.

TABLE 1 | Patient characteristics for the group with bacteremia and matched controls.

Characteristic	Bacteremia ($n = 52$)	Controls ($n = 52$)	<i>p</i> -Value
Age (years)	62.5 (51.5, 74.0)	61.5 (52.0, 71.0)	0.6
Male	33 (63.5%)	33 (63.5%)	>0.9
Female	19 (36.5%)	19 (36.5%)	>0.9
BMI (kg/m^2)	26.8 (24.1, 28.9)	27.4 (23.7, 30.9)	0.5
Obesity ($\text{BMI} \geq 30 \text{ kg}/\text{m}^2$)	10 (19.6%)	16 (32.0%)	0.2
Diabetes mellitus	16 (30.8%)	17 (32.7%)	>0.9
Charlson Comorbidity Index	5.0 (4.0, 7.0)	5.0 (3.0, 6.0)	0.3
Leukocytes ($\times 10^9/\text{L}$)	10.9 (7.9, 13.6)	7.0 (6.0, 8.9)	<0.001
Adiponectin ($\mu\text{g}/\text{mL}$)	3.5 (2.3, 6.0)	3.4 (1.8, 5.7)	0.6
Visfatin (ng/mL)	19.3 (9.5, 39.3)	10.3 (7.8, 18.6)	0.004
Resistin (ng/mL)	25.6 (10.9, 70.6)	13.8 (6.5, 20.5)	<0.001
APACHE II score	14.5 (10.0, 22.0)	NA	—
SAPS II score	29.0 (22.0, 40.0)	20.0 (14.0, 26.0)	<0.001
ICU admission	33 (63.5%)	11 (21.2%)	<0.001
Hospital mortality	10 (19.2%)	2 (3.8%)	0.03
Hospital length of stay (days)	34.0 (15.0, 69.0)	8.0 (5.0, 17.0)	<0.001

Note: Continuous data are presented as median (Q1, Q3), categorical data as n (%). *p* values are from Wilcoxon rank sum test for continuous data; Pearson’s chi-squared test for categorical data. *p*-values indicating statistical significance are shown in bold. Abbreviations: BMI, body mass index; ICU, intensive care unit.

Convalescent samples were obtained after resolution of infection (t_1) from $n = 35$ patients. Hospital mortality was 19.2% in cases versus 3.8% in controls ($p = 0.032$).

3.2 | Adipokine Profiles During and After Acute Bacteremia

Adiponectin was significantly higher during convalescence versus bacteremia (median 5.4 $\mu\text{g/mL}$ vs. 3.5 $\mu\text{g/mL}$, $p < 0.01$). Interestingly, we found no significant difference between bacteremia and controls (median 3.5 $\mu\text{g/mL}$ vs. 3.4 $\mu\text{g/mL}$), suggesting increased levels during convalescence (Figure 1A).

Visfatin showed elevated levels during bacteremia (median 19.3 ng/mL) compared to controls (10.3 ng/mL, $p = 0.01$), with no significant difference between bacteremia and convalescence, indicating sustained inflammatory activation during the convalescent phase (Figure 1B). As opposed to this sustained elevation, resistin levels were significantly elevated during bacteremia compared to controls (median 25.6 ng/mL vs. 13.8 ng/mL, $p < 0.001$) and normalized during convalescence (12.1 ng/mL, ns vs. controls), demonstrating an acute-phase response pattern (Figure 1C).

As expected, traditional inflammatory parameters were elevated during bacteremia: CRP was higher in the bacteremia group (median

134.0 mg/L) than both in the convalescence (17.3 mg/L) and control group (9.6 mg/L, both $p < 0.001$), confirming the acute systemic inflammatory activation (Figure 1D). IL-6 had a median value of 94 pg/mL during bacteremia and 40 pg/mL at convalescence (ns after correcting for multiple testing; data not shown). Directly comparing these trajectories highlights a dissociation between visfatin and the conventional acute-phase response. CRP and resistin move in parallel—both peak during bacteremia and fall toward the control range in convalescence—whereas visfatin remains elevated in convalescence despite their normalization. Visfatin thus appears to capture a sustained component of the host response that outlasts the acute inflammatory phase and is not reflected by CRP.

Figure 1 summarizes the adipokine and proinflammatory cytokine serum levels in the patient groups.

3.3 | Pathogen-Specific Differences at Baseline

We observed trends towards lower adiponectin and higher levels of proinflammatory biomarkers in patients with *S. aureus* bacteremia ($n = 37$) than in patients with bacteremia caused by other pathogens ($n = 15$) that failed to reach statistical significance ($p = 0.06$). Sample sizes were too small for further meaningful subgroup analyses. Table 2 summarizes pathogen-specific differences in adipokine serum levels and proinflammatory serum markers.

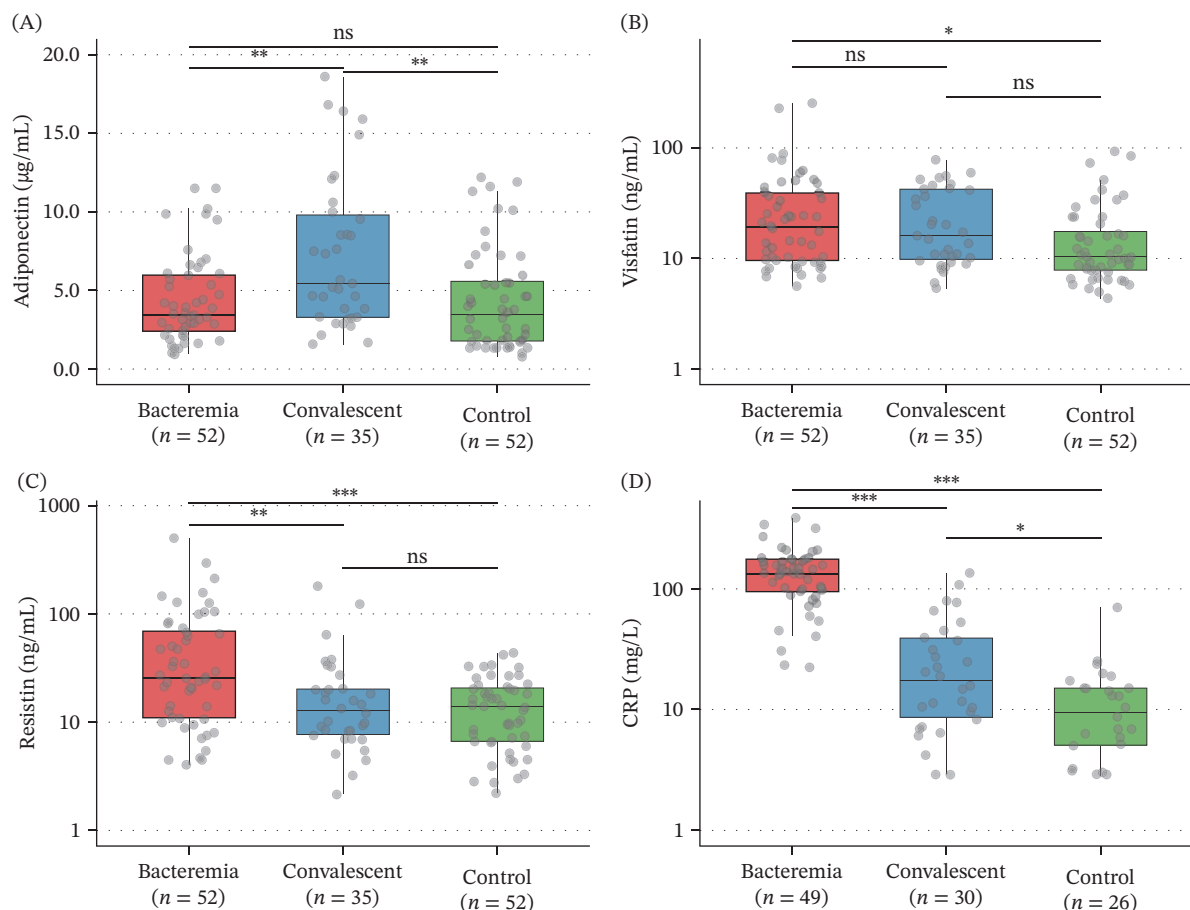


FIGURE 1 | Cytokine levels across study groups. Comparison of (A) adiponectin, (B) visfatin, (C) resistin, and (D) CRP concentrations among bacteremia patients (red), convalescent patients (blue), and controls (green). Box plots show median and IQR; gray dots show individual values. Sample sizes are indicated on the x-axis. Statistical comparisons: Wilcoxon rank-sum test with Bonferroni correction. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, ns = not significant.

TABLE 2 | Pathogen-specific serum adipokine levels for the groups with bacteremia caused by *S. aureus* versus other pathogens.

Biomarker	<i>S. aureus</i>	Other pathogens	<i>p</i> -Value
Adiponectin (µg/mL)	2.97 (2.15–5.25) (<i>n</i> = 37)	4.72 (3.71–6.54) (<i>n</i> = 15)	0.06
Visfatin (ng/mL)	22.61 (10.35–39.60) (<i>n</i> = 37)	11.55 (9.31–29.01) (<i>n</i> = 15)	0.23
Resistin (ng/mL)	26.89 (14.13–81.69) (<i>n</i> = 37)	23.80 (8.21–59.47) (<i>n</i> = 15)	0.23
CRP (mg/L)	136.00 (83.12–175.50) (<i>n</i> = 34)	134.00 (103.00–162.50) (<i>n</i> = 15)	0.96
IL-6 (pg/mL)	96.22 (44.55–247.80) (<i>n</i> = 37)	60.28 (40.91–140.90) (<i>n</i> = 15)	0.54

Note: Data are presented as median (Q1, Q3) with sample sizes. *p* values are from Wilcoxon rank sum test for continuous data.

3.4 | Correlation of Adipokine Serum Levels With Disease Severity in Patients With Bacteremia

Visfatin serum levels in bacteremia patients at baseline (*t*₀) significantly correlated with SAPS II scores (*n* = 52) (ρ = 0.333; *p* = 0.02; Figure 2B), while no significant correlation was found with adiponectin (ρ = −0.208; ns; Figure 2A) and resistin (ρ = 0.253; ns; Figure 2C). Moderate correlations were observed between individual adipokines and other disease severity

markers. Resistin correlated with APACHE II scores (ρ = 0.408; *p* = 0.02). Adiponectin demonstrated a significant inverse correlation with IL-6 (ρ = −0.397; *p* = 0.007; data not shown), consistent with the reciprocal relationship between anti-inflammatory and proinflammatory mediators.

The PLS analysis yielded the following combined adipokine score formula:

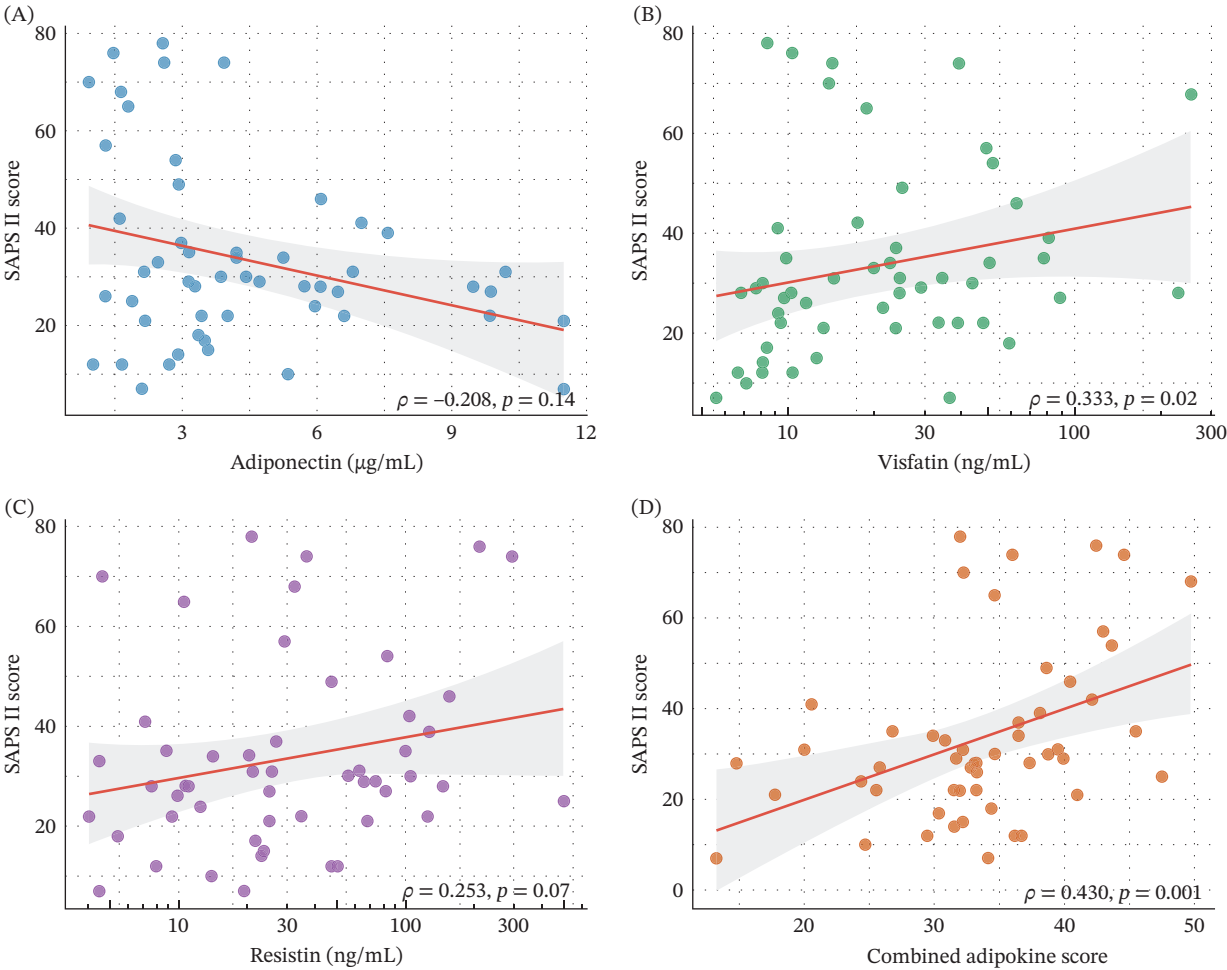


FIGURE 2 | Individual and combined adipokine correlations with disease severity as assessed by SAPS II score in bacteremia patients. Scatter plots showing adipokine concentrations versus SAPS II scores in bacteremia patients (*n* = 52). Individual subparts show: adiponectin on linear scale (A), visfatin on logarithmic scale (B), resistin on logarithmic scale (C), and PLS-derived combined adipokine score on linear scale (D). The combined score was derived using partial least squares regression to optimize correlation with SAPS II, incorporating standardized values of adiponectin (linear), log-transformed visfatin, and log-transformed resistin. Red lines represent linear regression fits with 95% confidence intervals (shaded areas). Correlation coefficients (ρ) are Spearman rank correlations with corresponding *p* values.

$$\begin{aligned}\text{Combined score} = & (-0.630 \times Z_{\text{Adiponectin}}) \\ & + (0.571 \times Z_{\text{log(Visfatin)}}) \\ & + (0.535 \times Z_{\text{log(Resistin)}}),\end{aligned}$$

where Z_X represents standardized values calculated as $(X - \text{mean})/\text{SD}$. Standardization parameters were as follows: adiponectin (mean = 4.37 $\mu\text{g/mL}$, SD = 2.79), log(Visfatin) (mean = 3.04, SD = 0.91), log(Resistin) (mean = 3.38, SD = 1.17). This combined score achieved superior correlation with SAPS II ($\rho = 0.430$; $p = 0.001$; Figure 2D), representing a 29% improvement over the strongest individual adipokine correlation. The weighting pattern reflected adiponectin's inverse association with severity (negative weight: -0.630) and positive contributions from visfatin (0.571) and resistin (0.535). The combined score thus captures the integrated adipokine dysregulation pattern and provides enhanced correlation with disease severity beyond the individual biomarker levels. Figure 2 summarizes the correlation analyses.

3.5 | Mortality Analysis

Among patients with bacteremia, in-hospital mortality was 19.2%. Among the evaluated biomarkers, CRP showed a significant association with in-hospital mortality: patients who died had higher CRP values at baseline (t_0) than survivors (214.9 mg/L vs. 124.7 mg/L, $p = 0.015$). No tested adipokine showed an individual association between initial adipokine level during bacteremia and mortality (resistin $p = 0.068$, adiponectin $p = 0.479$, visfatin $p = 0.353$; data not shown).

A “base” logistic regression model including age, sex, body mass index, and CRP was compared to a “full” model additionally incorporating the tested adipokines (adiponectin, visfatin, and resistin). The base clinical model achieved moderate discriminative performance (AUC = 0.784) to predict in-hospital mortality. In an exploratory analysis, the addition of adipokines to the base model resulted in improved discrimination in the full model (AUC = 0.944; $\Delta\text{AUC} = 0.159$). Likelihood ratio testing compared the nested models using the chi-square distribution ($\chi^2 = 11.89$, $\text{df} = 3$, $p = 0.008$). Model fit was assessed using the AIC, with the full model (with adipokines) showing superior fit (base AIC = 42.3 and full AIC = 36.4). As only 10 in-hospital deaths occurred, the model results should be interpreted with caution and hypotheses generated only. The superior fit suggests that added adipokine measurements may provide additional prognostic information to better predict mortality in bacteremia patients beyond conventional clinical parameters but requires confirmation in adequately powered cohorts.

4 | Discussion

Our data are consistent with adipokines that are distinctly altered during acute bacterial infections and in convalescence, with patterns that correlate with the disease severity. These findings not only contribute to the growing evidence supporting adipokines as biomarkers in severe infections beyond traditional inflammatory parameters but also highlight the interplay between inflammatory and metabolic pathways and point to a prominent role of adipose tissue as an active contributor to infection pathophysiology and to the resolution of an acute inflammatory state.

4.1 | Adipokine Response Patterns in Bacteremia

Adipokine patterns during bacterial bloodstream infections included elevated resistin and visfatin levels, while adiponectin was lower than during convalescence. In critically ill patients with sepsis, both resistin and visfatin have been described as elevated, and adiponectin as either unaffected or reduced (reviewed in [8]). The resistin elevation during acute bacteremia, followed by normalization during convalescence, indicates a role as an acute-phase reactant. This is in line with publications showing that resistin is part of an inflammatory cytokine network during the acute phase of sepsis, involving IL-6, IL-8, IL-10, and MCP-1 [14]. The elevation of visfatin persisted into the convalescence phase and suggests a slightly different pathophysiological role, possibly reflecting ongoing cellular metabolic stress and energy dysregulation that extend beyond acute inflammation. This observation is consistent with visfatin's role in activating immune cells through p38 and MEK1 pathways while simultaneously regulating cellular NAD metabolism during stress conditions [15].

Adiponectin levels were lower during bacteremia compared to convalescence but similar to controls. This pattern could reflect either an increase of adiponectin during recovery as part of anti-inflammatory regulation or alternatively a loss of anti-inflammatory adipokine during the acute phase of infection. This finding is consistent with previous observations that adiponectin levels are suppressed after staphylococcal infection in vitro [11] and during experimental sepsis as well as in sepsis patients [10, 23]. Interestingly, we also observed a significantly higher inflammatory burden (CRP) and a trend towards more pronounced adiponectin suppression in infections caused by *S. aureus* compared to other pathogens. *S. aureus*-specific virulence mechanisms may contribute to this observation, including its ability to survive intracellularly within 3T3 adipocytes (among others), leading to reduced adiponectin and resistin and increased visfatin secretion [11]. These pathogen-specific interactions suggest that bacterial species or different bacterial components may trigger distinct metabolic and/or inflammatory pathways. Future studies will have to elaborate on these observations.

The adiponectin suppression associated with infection likely involves multiple mechanisms, including IL-6-mediated downregulation, as underlined by a negative correlation between adiponectin and IL-6 levels. Of note, adiponectin levels in control patients (that were hospitalized for noninfectious causes) might have been reduced due to other underlying diseases by disease-specific cytokines in a similar way. Overall, the changes in the adipokine profile during bacteremia could support the initial immune response by promoting glucose availability to metabolically active immune cells while simultaneously contributing to the insulin resistance observed during the acute phase of severe infections.

4.2 | Correlation With Disease Severity and Mortality

Multiple studies have evaluated adipokine serum levels as potential biomarkers in acute inflammation. Particularly, visfatin has been correlated with disease severity, organ failure, and mortality in critically ill patients [16]. In acute pancreatitis, both visfatin and resistin correlate with clinical severity and predict peripancreatic necrosis [24, 25]. In our study, individual adipokines were only

moderately correlated with the disease severity. A PLS-combined adipokine score, however, demonstrated a stronger correlation with disease severity than any individual adipokine (Figure 2D). Matching the up- or downregulation of specific cytokines during bacteremia, adiponectin levels were represented with a negative and visfatin/resistin with positive weights in the PLS combined score.

The enhanced performance of the combined adipokine score may reflect the complex nature of metabolic-immune responses during severe infections, where multiple cytokine/adipokine pathways are simultaneously dysregulated. The combined approach could capture the integrated adipokine dysregulation pattern that occurs during bacterial infection, where the adipose tissue undergoes fundamental reprogramming from metabolic regulation toward immune activation, both on a local and a systemic level. Locally, for example, adipocytes surrounding draining lymph nodes have been shown to initiate transcriptional responses indicative of IFN- γ stimulation and a shift away from lipid metabolism toward immunologic function following bacterial infection, partly through NOD1-dependent sensing of intracellular bacteria [26]. Additionally, adipocytes directly participate in infection control via the production of antimicrobial peptides [19, 27]. Systemically, obesity has been associated with favorable outcomes in systemic inflammatory states (so-called “obesity paradox”), potentially via so-called “browning” of white adipose tissues [28]. However, these observations are hampered by methodological problems and are contradicted by other observations, in which visceral obesity is associated with worse outcomes [29–31]. Consequently, the role of adipose tissue in acute systemic inflammation to date is ill defined, and future research is urgently warranted.

Our mortality analysis revealed that among individual biomarkers, CRP showed the strongest association with in-hospital mortality, while individual adipokines showed weaker associations. The addition of adipokines to clinical parameters in logistic regression models resulted in improved discrimination for mortality prediction, suggesting a unique capacity of adipokines to integrate both metabolic and inflammatory information during severe infections. Given the single-center design and modest sample size, though, both the combined score and the addition of adipokines as prognostic markers should be regarded as a proof-of-concept requiring external validation.

4.3 | Pathophysiological and Clinical Implications

The coordinated adipokine response pattern observed in this study together with previous ex vivo data indicates that immunometabolic responses represent integral components of infection pathophysiology beyond mere sequelae of systemic inflammation [32]. In this context, adipose tissue functions as an immunometabolic organ including resident macrophages and dendritic cells that respond rapidly to pathogen-associated molecular patterns, transforming from metabolic regulation toward immune activation [33]. Notably, adipocytes themselves express most innate immune pattern recognition receptors [33]. The observed adipokine changes could reflect this fundamental change in adipose tissue function during bacterial infection.

The pathophysiological significance extends beyond mere systemic proinflammatory signaling to direct effects on local

immune function and even bacterial clearance for some pathogens [19, 27]. Resistin elevation may initially support immune responses through enhanced cytokine production and metabolic changes that redirect glucose towards immune cells. Prolonged resistin elevation, however, contributes to insulin resistance and glucose intolerance that may become disadvantageous during recovery [13, 34]. Similarly, visfatin’s dual role in immune activation and NAD metabolism suggests that its persistent elevation reflects cellular mechanisms to maintain energy homeostasis during metabolic stress during infection and convalescence, though chronic elevation may contribute to sustained metabolic dysfunction [35].

The acute suppression of adiponectin is likely an important part of the pathophysiological alteration of the adipose tissue caused by bacterial infections. Adiponectin is one of the most abundant adipokines, and this anti-inflammatory mediator has been implicated in enhanced bacterial clearance, inhibition of cytokine production, and promoting the resolution of inflammation while controlling insulin sensitivity [6, 10, 36]. The increased suppression in infections caused by *S. aureus* may either be pathogen-specific, attributable to divergent underlying diseases (e.g., deep tissue infections), or correlate with more severe infections (and inflammation) in these infections. Our observations are consistent with animal studies showing distinct adipokine responses to *S. aureus* infection [37]. The ability of *S. aureus* to survive within adipocytes and alter their secretory profile [11] also suggests a complex host–pathogen interaction where bacterial persistence within metabolic tissues could contribute to systemic metabolic dysfunction.

Clinical implications include the recognition that metabolic complications such as hyperglycemia and insulin resistance during severe infections such as bacteremia and/or sepsis may partially result from adipokine dysregulation rather than solely reflecting glycemic management issues due to acute-phase reactants: changes in adipokine levels contribute to insulin resistance in critically ill patients, with alterations similar to those seen in obesity [5]. Persistent systemic adipokine alterations such as prolonged visfatin elevation during convalescence from systemic bacterial infections suggest that these alterations extend beyond the resolution of acute inflammation. This observation may also have relevance for postinfectious complications such as post-sepsis syndrome and long-term metabolic complications observed in sepsis survivors.

In the long run, innovative therapeutic advances are also conceivable from understanding infection-induced adipokine pathophysiology. One could speculate that modulation of adiponectin (either through GLP-1 or adiponectin receptor agonists, reviewed in [12]) may develop into a therapeutic target for restoring an anti-inflammatory balance. Pending clinical translation, modulation of NAD metabolism through visfatin/NAMPT pathway targeting may additionally influence both immune function and metabolic recovery.

4.4 | Strengths, Limitations, and Future Research

Strengths of this study include the prospective matched case-control study design reducing confounders, a comprehensive

assessment of adipokines including a recovery timepoint and additional controls, and the application of a novel combined adipokine scoring. The inclusion of both acute and convalescent samples provides insights into the temporal dynamics of adipokine responses that single-timepoint studies cannot address. Limitations include the single-center design with a limited sample size that restricted statistical power, particularly for mortality analysis ($n = 10$ deaths). The timing of blood sampling relative to symptom onset was not standardized and may have influenced our results, especially by attenuating or adding noise to the associations observed. Serial measurements during the acute phase would have allowed us to assess early kinetic changes. The lopsided pathogen distribution (71.2% *S. aureus*) may limit generalizability to other bacterial infections, though it provided the opportunity for pathogen-specific analysis. A Gram-stratified subgroup analysis, however, was not feasible and would require larger cohorts. The study population's characteristics and healthcare system factors may influence its applicability to other clinical settings.

Our results point to several avenues for future research. The timing of blood sampling relative to infection onset was not standardized (median, 3 days). Adipokine levels, particularly those as acute-phase reactants, may differ depending on whether samples were obtained at the peak inflammatory response versus early resolution. Serial sampling with standardized time points could also optimize the understanding of adipokine kinetics and their relationship to clinical trajectories. The integration of metabolomics as well as adipose tissue histology/immunohistochemistry in different fat depots with adipokine measurements may reveal broader metabolic patterns that contribute to sepsis pathophysiology. Larger multicenter studies are needed to validate findings across diverse populations and healthcare systems and to standardize assays and population-specific reference ranges (which are lacking). The future integration of additional patient-related factors such as body composition, sex, or genetic polymorphisms could explain the variability in adipokine responses and identify patients most likely to benefit from adipokine-targeted interventions. Finally, therapeutic trials investigating metabolic modulators in patients with severe infections would be the translational step from mechanistic understanding toward clinical applications.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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