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Circulating eNampt and resistin as a proinflammatory duet predicting independently mortality in critically ill patients with sepsis: A prospective observational study

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ABSTRACT

Background: The adipocytokines eNampt and resistin are involved in the regulation of inflammation exerting pro-inflammatory actions. Our aim was to jointly investigate whether circulating eNampt and resistin, and their kinetics predict 28-day mortality of sepsis.

Methods: In a prospective study, serum eNampt and resistin were determined in 102 critically ill patients fulfilling the diagnostic criteria of SEPSIS-3, at enrollment and one week after, and in 102 healthy controls matched on age, gender and month of diagnosis.

Results: Serum eNampt and resistin were significantly higher in septic patients than controls ($p < 0.001$), and higher in septic shock compared to sepsis ($p < 0.001$). Both eNampt and resistin decreased significantly during the first week of sepsis ($p < 0.001$). However, patients with septic shock presented a sustained elevation of eNampt and resistin compared to patients with sepsis. Both adipocytokines were positively correlated with sepsis severity scores and lactate. Baseline eNampt was a better discriminator of sepsis and septic shock compared to C-reactive protein and procalcitonin. Serum eNampt and resistin were higher in nonsurvivors than in survivors during the first week of sepsis. Prolonged and sustained elevation of both eNampt and resistin, as reflected by a lower percentage change from their baseline values, was independently associated with 28-day mortality (HR: 0.05, 95% C.I. 0.01–0.28, $p = 0.001$; HR: 0.19, 95% C.I. 0.07–0.50, $p = 0.001$, respectively), after adjustment for significant clinical and laboratory biomarkers.

Conclusion: Circulating eNampt and resistin, and their kinetics may represent useful diagnostic and prognostic biomarkers in critically ill septic patients. More prospective studies are needed to elucidate their ontological and pathophysiological role in sepsis.

1. Introduction

Sepsis is the most lethal complication of infection and constitutes the leading cause of death due to infection in critically ill patients [1,2]. It is characterized by a dysregulated systemic inflammatory response, which leads to life-threatening organ dysfunction [3]. Early diagnosis

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; aPTT, activated Partial Thromboplastin Time; BMI, Body Mass Index; CI, Confidence Interval; CRP, C-reactive protein; CV, Coefficient of Variation; ELISA, Enzyme Linked ImmunoSorbent Assay; eNampt, extracellular nicotinamide phosphoribosyl transferase; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; HR, Hazard Ratio; ICU, Intensive Care Unit; IL, Interleukin; INR, International Normalized Ratio; LDL-C, low-density lipoprotein cholesterol; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NAD, nicotinamide adenine dinucleotide; NF-κB, nuclear factor κB; PCT, procalcitonin; PBEF1, pre-B-cell colony-enhancing factor 1; ROC, Receiver Operating Characteristic; SOFA, Sequential Organ Failure Assessment score; suPAR, soluble urokinase-type Plasminogen Activator Receptor; TLR-4, toll-like receptor 4; TNF-α, Tumor Necrosis Factor-alpha

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and treatment can improve outcome, but reliable sepsis biomarkers are lacking.

Adipose tissue has now emerged as a genuine endocrine organ secreting bioactive molecules, termed adipocytokines [4,5]. Both *in vitro* and *in vivo* studies have shown that adipocytokine expression is altered in chronic as well as in acute inflammatory states like sepsis [4,6]. Among adipocytokines, extracellular nicotinamide phosphoribosyl transferase (eNampt), also known as pre-B-cell colony-enhancing factor 1 (PBEF1) or visfatin, and resistin are involved in the regulation of inflammation, exerting pro-inflammatory actions [5,7]. eNampt is mainly expressed by activated lymphocytes, neutrophils and macrophages, and plays an active role in the regulation of immunity and inflammation, displaying various proinflammatory actions, such as activation of B-cells, T-cells and monocytes, induction of inflammatory cytokines expression and inhibition of neutrophil and macrophage apoptosis [7,8]. Moreover, eNampt expression is upregulated in neutrophils and monocytes by lipopolysaccharide (LPS) and proinflammatory cytokines (IL-1β, IL-6, TNF-α) [7]. In accordance with translational data, clinical studies have shown that eNampt is increased in various chronic and acute inflammatory diseases [9,10], being also associated with acute lung injury in septic patients [11].

Resistin, a proinflammatory molecule originally reported as an adipocyte-derived hormone in mice, is predominantly produced by monocytes and macrophages in the visceral adipose tissue in humans [12]. Resistin competes with LPS for binding to Toll-like receptor 4 (TLR-4) [13] and induces the release of IL-1β, IL-6, IL-12 and TNF-α from monocytes and macrophages, through activation of the nuclear factor κB (NF-κB) pathway [14,15]. Furthermore, resistin is upregulated by interleukins and LPS like eNampt [16]. Hyperresistinemia characterizes various metabolic, cardiovascular and neoplastic diseases [15,17], chronic inflammatory and autoimmune diseases [18], and sepsis [6,19,20]. Recent studies have found an association of resistin with the severity of sepsis but very few have investigated its kinetics [19,21–23] and prognostic value in sepsis [19,20].

To date, no study has jointly examined eNampt and resistin in critically ill patients with sepsis. In this context, we aimed to simultaneously investigate the kinetics of adipocytokines eNampt and resistin in sepsis and their association with severity and mortality, in a prospective study. Another goal was to compare serum baseline eNampt and resistin levels in septic patients and healthy controls as well as to explore their association with clinical, inflammatory and metabolic biomarkers.

2. Material and methods

2.1. Study population and protocol

This prospective case-control study was conducted in the multivalent adult medical/surgical ICU of a tertiary teaching hospital between August 2013 and July 2015. The study protocol has been published in our previous work [24]. We prospectively studied 102 consecutive patients fulfilling the criteria of sepsis or septic shock according to SEPSIS-3 [3], within 48 h from sepsis onset, who were hospitalized in the ICU for at least one week after inclusion to the study. Based on these criteria, sepsis was diagnosed in patients with a suspected or proven infection and an acute increase in SOFA score of ≥2 points. Septic shock was diagnosed in patients with sepsis presenting with persistent hypotension requiring vasopressors to maintain a mean arterial pressure ≥65 mmHg and having a serum lactate level > 2 mmol/L despite adequate volume resuscitation. We excluded patients who were below 18 years, were pregnant, had a history of diabetes, malignancy, HIV infection, neutropenia defined as an absolute neutrophil count below 1000/mm^3 attributed to causes other than sepsis, immunosuppressive therapy or radiation and a history of chronic steroid use, defined as daily intake > 0.4 mg/kg of equivalent prednisone for > 15 days. The flow diagram of patient enrollment is shown in Fig. 1. Patients were treated according to the Surviving Sepsis Campaign clinical guidelines [2] and were followed for 28 days. We recorded demographic, clinical and laboratory data. We also enrolled 102 apparently healthy overnight-fasted controls (57 men, 45 women; mean age: 66.4 ± 10.3 years; mean BMI: 28.1 ± 5.01 kg/m^2) with no history of malignancy, infection or diabetes, who came for an annual check-up examination at the Outpatient Clinic of the Laboratory Department of the same hospital. Controls had normal values for blood counts, CRP and liver enzymes. For every eligible case, an attempt was made to randomly identify a control as closely as possible in time to the admission of the corresponding case (± 1 month) and matched to cases on age (± 5 years) and gender. The study was approved by the Scientific and Ethical Committee of the hospital (#587/10-04-2013). Informed consent was given by all study participants or their next of kin.

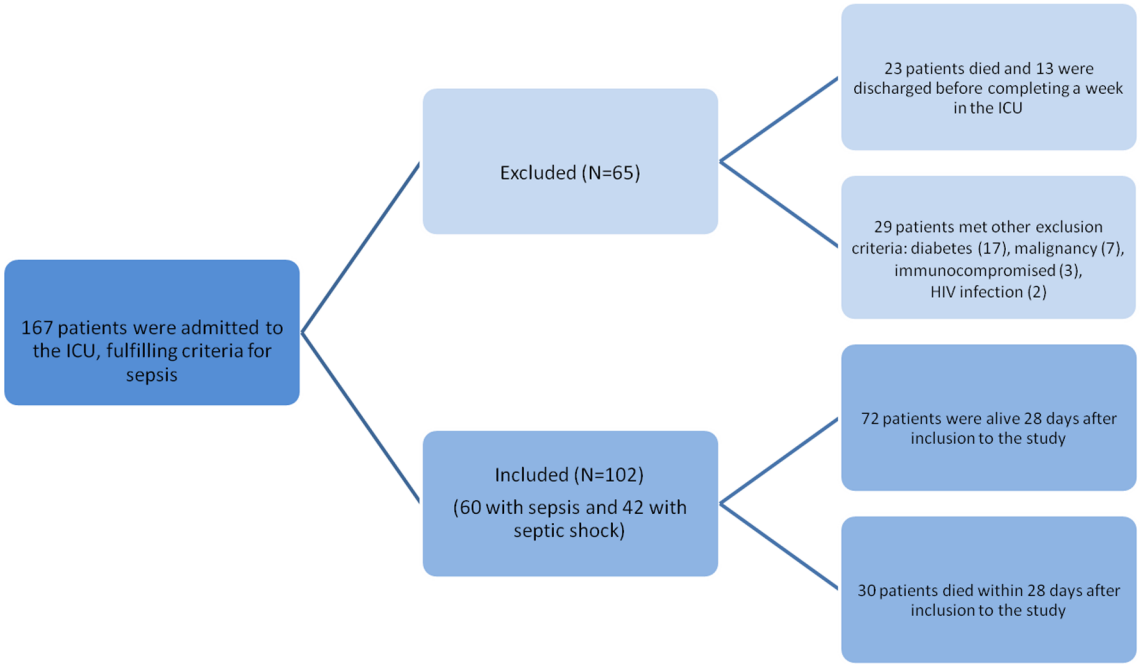

Fig. 1. Flow diagram of patient enrollment.

2.2. Laboratory evaluation

Blood collection of septic patients for determination of adipocytokines and cytokines was performed upon enrollment to the study and one week after enrollment. Blood was collected from controls upon enrollment to the study. All specimens were centrifuged and sera were frozen at −80 °C. Serum eNampt and resistin were determined using commercially available enzyme linked immunosorbent assays (Phoenix Pharmaceuticals Inc, Burlingame, CA 94010, USA) according to the manufacturers' instructions as previously described [17,25–28]. Concentrations of IL-6, IL-10, IL-1β, TNF-α and soluble urokinase-type Plasminogen Activator Receptor (suPAR) were measured using ELISA as previously described [24,29]. Serum insulin and procalcitonin were determined using electro-chemiluminescent immunoassays (Cobas, Roche Diagnostics Corporation, Indianapolis, Indiana, USA). Coagulation biomarkers, glucose, creatinine, protein, albumin, lactate, lipid parameters (total cholesterol, LDL-C, HDL-C, triglycerides) and CRP were measured using automated analyzers as previously described [24,29,30]. HOMA-IR (Homeostasis model assessment score of insulin resistance) was calculated using the formula: fasting serum insulin (μU/ml) × fasting serum glucose (mmol/l)/22.5.

2.3. Statistical analysis

Data were examined using chi-square test for categorical variables; *t*-test and paired *t*-test for normally distributed variables; and Mann-Whitney U and Wilcoxon matched-pair tests for not normally distributed variables. Normality hypothesis was evaluated using the Shapiro-Wilk test. Spearman correlation coefficients (r) were used as measurements of correlation for continuous variables. To explore discriminative values, we calculated the areas under the Receiver Operating Characteristic (ROC) curves for variables significantly differing between sepsis and septic shock. Survival curves resulted using the Kaplan-Meier method and comparisons were performed using the log rank test. The discriminating power of measured biomarkers as mortality predictors was obtained by assessing ROC curves. In order to identify the independent laboratory predictors of 28-day mortality, particularly the percentage change of predictors (that is the difference Δ between variable at one week after enrollment and baseline variable divided by baseline variable, expressed in percentage), a multivariate Cox-regression analysis was performed adjusting for important clinical parameters defined *a priori* (age, gender, BMI, APACHE II and presence of septic shock) and statistically significant laboratory predictors. For data clarity, because no currently clinically relevant cutoffs have been accepted for eNampt or resistin, quartiles of all laboratory biomarkers were incorporated in the models. A two-sided p value of less than 0.05 was considered significant. Statistical analysis of the data was performed using IBM-SPSS® version 24 for Windows.

3. Results

3.1. Baseline clinical and laboratory data

Table 1 depicts baseline clinical and laboratory features from the entire cohort of septic patients. The 28-day mortality rate was 57% for septic shock and 10% for sepsis patients. According to ICU admission diagnosis, 61 (59.8%) were medical cases, 29 (28.4%) were surgical cases and 12 (11.8%) were trauma cases. The most frequent type of infection was pneumonia (n = 36) followed by abdominal infections (n = 24). The following pathogens were isolated in 60 (58.8%) patients: Gram-negative bacteria in 36 (16 *Acinetobacter species*, 8 *Klebsiella pneumonia*, 10 *Pseudomonas species,* 1 *Escherichia coli* and 1 *Providencia stuartii*), Gram-positive in 14 (6 *Staphylococcus aureus*, 8 *Coagulase Negative Staphylococci*) and *Candida species* in 10 patients.

3.2. Circulating eNampt and resistin in patients and controls

On admission, septic patients exhibited a significantly higher mean eNampt level (79.06 ± 19.54 μg/L vs 44.92 ± 27.56 μg/L, p < 0.001) along with a significantly elevated mean resistin level (36.45 ± 13.58 μg/L vs 9.42 ± 6.52 μg/L, p < 0.001) compared to controls (Fig. 2). The significant differences in eNampt and resistin levels remained unchanged after adjusting for age, gender and BMI (p < 0.001 and p = 0.01 respectively).

Table 1
Clinical and laboratory baseline variables of septic patients (N = 102).

Variables*	
Age[a], years	64.7 ± 15.6
Gender, male, n (%)	57 (55.9)
Death before day 28, n (%)	30 (29.4)
Presence of septic shock, n (%)	42 (41.2)
BMI[a], kg/m^2	29.9 ± 8.5
APACHE II score[a]	23 ± 7.2
SOFA[a]	10 ± 3.3
Hematologic parameters	
Hemoglobin[a], g/L	93 ± 20
White Blood Cells[a] x10^9/L	14.058 ± 8.397
Neutrophils[a] x10^9/L	11.478 ± 7.920
Platelets[a] x10^9/L	216.2 ± 118.8
Metabolic and Coagulation biomarkers	
Albumin[a], g/L	24.6 ± 5.9
Lactate[b], mmol/L	2.1 (1–9)
Creatinine[a] μmol/L	123.76 ± 70,72
Protein[a], g/L	50 ± 9
Glucose[a], mmol/L	7.97 ± 2.9
Insulin[b], pmol/L	197.93 (88.2–402.81)
HOMA-IR[b]	8.9 (3.24–34.5)
Triglycerides[a], mmol/L	2.09 ± 1.17
Total Cholesterol[a], mmol/L	2.95 ± 0.99
LDL-Cholesterol[a], mmol/L	1.39 ± 0.92
HDL-Cholesterol[a], mmol/L	0.52 ± 0.49
Prothrombin time[a], sec	14.3 ± 4.7
aPTT[a], sec	38.9 ± 9.4
Fibrinogen[a], μmol/L	14.49 ± 5.26
Classic biomarkers of sepsis	
CRP[b], nmol/L	1,257 (67–4,105)
Procalcitonin[b], μg/L	0.9 (0.1–100)
Adipocytokines	
Resistin[a], μg/L	36.45 ± 13.58
eNampt[a], μg/L	79.06 ± 19.54
Cytokines	
IL-1β[b], ng/L	5.9 (5.9–206)
IL-6 [b] ng/L	27.4 (6–444)
IL-10[b], ng/L	5 (5–300)
TNF-α[b], ng/L	6 (6–337)
suPAR[b], μg/L	13 (2.1–16.8)

APACHE II, acute physiology and chronic health evaluation score; aPTT, activated Partial Thromboplastin Time; BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IL, interleukin; LDL, low-density lipoprotein; SOFA, sequential organ failure assessment score; suPAR, soluble urokinase-type plasminogen activator receptor; TNF-α, tumor necrosis factor alpha.

* Values of normally distributed variables are reported as mean ± SD, and those of non-normally distributed variables are reported as median (range).

[a] Mean ± SD.

[b] Median, range.

3.3. Circulating eNampt and resistin kinetics in septic patients according to sepsis severity

Patients with septic shock presented significantly higher serum eNampt and resistin compared to patients with sepsis (p < 0.001), both at baseline and day 7 (p < 0.001) (Table 2). The whole patient cohort manifested a significant decrease in mean serum eNampt and resistin levels from enrollment to day 7 (p < 0.001). However, patients with septic shock showed a sustained elevation of eNampt and resistin from baseline to day 7 compared to patients with sepsis because the

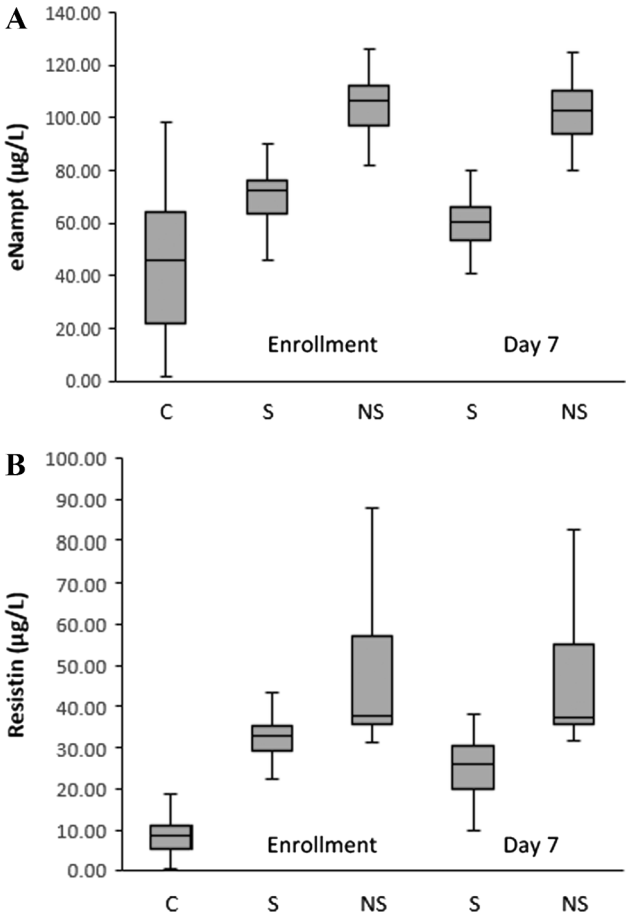

Fig. 2. Box plots of serum eNampt and resistin at enrollment and one week after stratifying by 28-day mortality status. A. On admission, septic patients present a significantly elevated mean eNampt (79.06 ± 19.54 μg/L vs 44.92 ± 27.56 μg/L, $p < 0.001$) compared to controls (C). eNampt levels are significantly higher in nonsurvivors (NS) than survivors (S) both at enrollment (101.67 ± 17.74 μg/L vs 69.63 ± 10.61 μg/L, $p < 0.001$) and day 7 (99.08 ± 17.72 μg/L vs 59.59 ± 8.96 μg/L, $p < 0.001$). The decrease in eNampt from baseline to day 7 is significant in both groups of patients ($p < 0.001$). B. On admission, septic patients present a significantly elevated mean resistin level (36.45 ± 13.58 μg/L vs 9.42 ± 6.52 μg/L, $p < 0.001$) than controls (C). Resistin levels are significantly higher in nonsurvivors (NS) than survivors (S) septic patients both at enrollment (48.13 ± 17.55 μg/L vs 31.58 ± 7.40 μg/L, $p < 0.001$) and day 7 (46.20 ± 16.04 μg/L vs 25.22 ± 7.37 μg/L, $p < 0.001$). The decrease in resistin from baseline to day 7 is significant in both groups of patients ($p = 0.005$ for NS, $p < 0.001$ for S).

decrease (expressed as percentage change from baseline values) in eNampt and resistin was significantly pronounced only in patients with sepsis compared to patients with septic shock (ΔeNampt%: 13.3 ± 6% vs 7.3 ± 6.4%, $p < 0.001$; Δresistin%: 20 ± 14.4% vs 11.7 ± 8.6%, $p = 0.003$, respectively).

3.4. Sepsis discrimination

ROC curves were generated for eNampt and resistin as well as for sepsis-related biomarkers with significant p-values (Fig. 3). Circulating baseline eNampt and CRP outperformed resistin, procalcitonin, IL-6, IL-10 and suPAR in discriminating sepsis from septic shock (Table 3).

3.5. Correlations between eNampt, resistin and laboratory biomarkers

Circulating eNampt exhibited significantly positive correlations with resistin, APACHE II, SOFA score, lactate, white blood cells, neutrophils, coagulation parameters (INR, aPTT), creatinine and procalcitonin at baseline and one week after and with baseline CRP, IL-10, glucose, insulin and HOMA-IR. On the contrary, eNampt correlated negatively with total protein and albumin (Table 4a). Resistin presented significantly positive correlations with eNampt, APACHE II, SOFA score and lactate at baseline and one week after, with baseline insulin, HOMA-IR, IL-6, IL-10 and TNF-α and with white blood cells, neutrophils and procalcitonin one week after. Resistin correlated negatively with total protein and albumin, only one week after sepsis onset (Table 4b). Baseline eNampt did not present any significant correlations with BMI, lipid parameters, platelets, IL-1β, IL-6, TNF-α or suPAR, while baseline resistin did not show any significant correlations with BMI, lipid parameters, glucose, CRP, procalcitonin, IL-1β, TNF-α or suPAR ($p > 0.05$).

3.6. Circulating eNampt, resistin and mortality

Mean serum eNampt and resistin were higher in nonsurvivors than in survivors both at baseline and on day 7 as shown in Fig. 2 ($p < 0.001$). Both groups of patients exhibited a significant decrease in eNampt and resistin from enrollment to day 7 ($p < 0.001$). Nevertheless, the percentage change was significant only in survivors compared to nonsurvivors (ΔeNampt%: 14.3 ± 5% vs 2.6 ± 1.8%, $p < 0.001$; Δresistin%: 20.9 ± 12.8% vs 6.2 ± 5%, $p < 0.001$).

Subjects with significant percentage changes in serum eNampt and resistin from baseline to day 7 manifested improved survival compared to those with lower percentage changes (Fig. 4). In unadjusted Cox-regression models, elevated circulating eNampt and resistin levels, both at enrollment and day 7, were associated with mortality ($p < 0.001$). At enrollment, after adjustment for clinical parameters (age, gender, BMI, APACHE II, HOMA-IR and presence of septic shock) and significant laboratory biomarkers (yielded from univariate analyses: CRP, IL-6 and WBC), elevated eNampt (HR: 3.40, 95% C.I. 1.77–6.50, $p < 0.001$) and resistin (HR: 3.78, 95% C.I. 1.60–8.91, $p = 0.002$) were associated with mortality. At day 7, after adjustment for the abovementioned variables, Cox-regression model produced similar results with higher eNampt (HR: 12.26, 95% C.I. 3.69–40.68, $p < 0.001$) and resistin (HR: 4.42, 95% C.I. 1.36–14.36, $p = 0.013$) being associated with mortality. Interestingly, regarding kinetics, both lower percentage change in eNampt (HR: 0.05, 95% C.I. 0.01–0.28, $p = 0.001$) and resistin (HR: 0.19, 95% C.I. 0.07–0.50, $p = 0.001$) levels from baseline values were independently associated with mortality adjusting for clinical and significant laboratory biomarkers yielded from univariate analysis. Results are shown in Table 5.

4. Discussion

In this prospective study, we investigated two proinflammatory adipocytokines, eNampt and resistin, in critically ill patients with sepsis. We found that both were significantly increased compared to healthy controls, while their levels were significantly higher in septic shock than sepsis. Based on their kinetics during the first week from sepsis onset, the key finding of our study was that the sustained elevation of both eNampt and resistin was significantly associated with the severity of sepsis as well as the 28-day mortality. Remarkably, the lower kinetics of both adipocytokines was independently associated with mortality after adjusting for significant clinical and laboratory biomarkers. To the best of our knowledge, this is the first study to demonstrate an independent association between lower serum eNampt and resistin kinetics and sepsis mortality.

Our results are in agreement with two clinical studies demonstrating higher eNampt levels in nonsurvivors than survivors and a positive correlation with sepsis severity in critically ill patients [31,32]. Only one retrospective study has demonstrated an independent association of serum eNampt at admission with hospital mortality [31]. However, these studies determined eNampt only upon admission and did not explore eNampt kinetics in sepsis. Furthermore, they had either a small

Table 2
Main laboratory biomarkers* of patients with sepsis and septic shock, at baseline and one week after admission.

	At admission			One week after admission		
	Sepsis (n = 60)	Septic shock (n = 42)	p-value	Sepsis (n = 60)	Septic shock (n = 42)	p-value
Hematologic parameters						
White Blood Cells[a] x10^9/L	12,486 ± 5,944	16,304 ± 10,680	0.02	8,494 ± 3,210	16,163 ± 11,072	< 0.001
Platelets[a] x10^9/L	230.4 ± 117.6	195.8 ± 118.8	0.15	252.7 ± 120.3	174.6 ± 97.94	0.001
Markers of organ function						
Albumin[a], g/L	26 ± 5.6	22.6 ± 5.7	0.004	25.1 ± 4.8	22.5 ± 4.2	0.005
Lactate[b], mmol/L	1.2 (1–5)	2.4 (2.1–9)	< 0.001	1 (1–2.7)	1.9 (0.7–19)	< 0.001
Classic sepsis biomarkers						
CRP[b], nmol/L	848 (67–2,076)	1,667 (344–4,105)	< 0.001	524 (76–2,686)	962 (124–2,410)	0.01
Procalcitonin[b], μg/L	0.7 (0.09–47.7)	4.8 (0.14–100)	0.002	0.5 (0.06–15)	1.4 (0.14–83)	0.001
Adipocytokines						
Resistin[a] μg/L	33.4 ± 13.6	40.8 ± 12.4	< 0.001	27.4 ± 13.9	37.1 ± 12.8	< 0.001
eNampt[a,] μg/L	70.4 ± 13.9	91.4 ± 19.8	< 0.001	61.2 ± 14.4	85.5 ± 22.6	< 0.001
Cytokines						
IL-1β[b], ng/L	5.9 (5.9–207)	8.8 (5.9–44.8)	0.18	17 (5.9–499)	8.8 (5.9–45)	0.13
IL-6 [b], ng/L	16.5 (6–385)	74.4 (10–444)	0.001	25 (4.6–419)	20.5 (6–487)	0.34
IL-10[b], ng/L	5 (5–300)	6.9 (5–87)	0.001	5 (5–300)	5 (5–66)	0.02
TNF-α[b], ng/L	6 (6–240)	6 (6–337)	0.29	6 (6–812)	6 (6–261)	0.91
suPAR[b], μg/L	10.5 (2.2–16.8)	14.1 (4.4–16.8)	0.04	11.3 (2.6–16.8)	12.9 (5.2–16.8)	0.68

CRP, C-reactive protein; IL, interleukin; suPAR, soluble urokinase-type plasminogen activator receptor; TNF-α, tumor necrosis factor alpha.
* Values of normally distributed variables are reported as mean ± SD, and those of non-normally distributed variables are reported as median (range).
[a] Mean ± SD.
[b] Median, range.

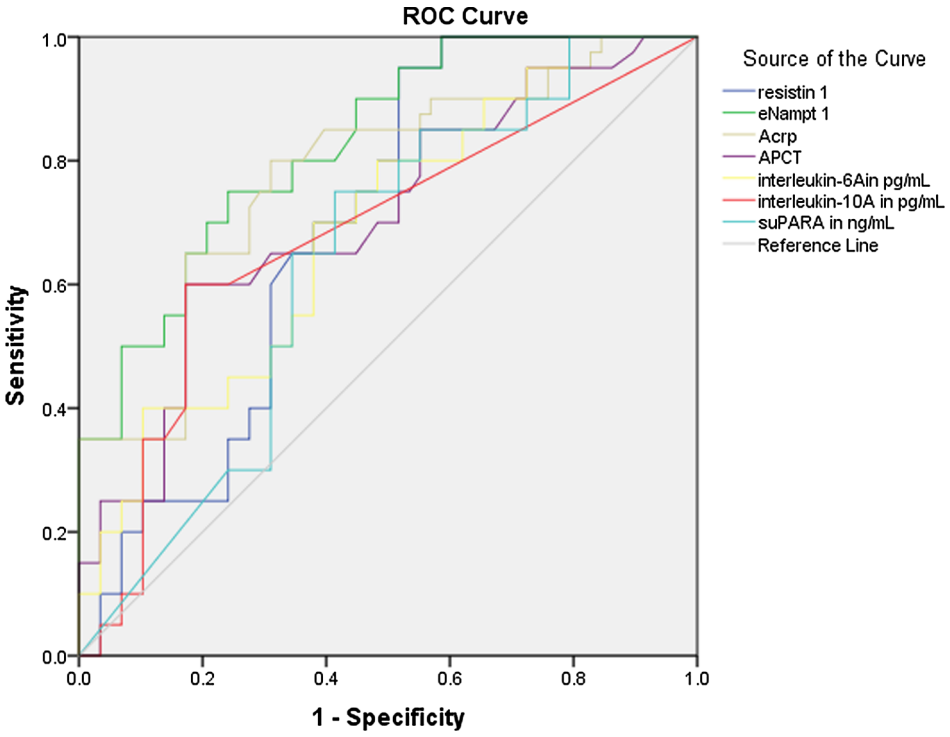

Fig. 3. Area under the Receiver Operating Characteristic Curve (AUROC) discriminating sepsis from severe sepsis in 102 patients with sepsis. Circulating eNampt (AUROC > 0.83) and C-Reactive Protein (AUROC > 0.78) at admission outperform procalcitonin (AUROC > 0.71), resistin (AUROC > 0.69), IL-6 (AUROC > 0.69), IL-10 (AUROC > 0.68) and suPAR (AUROC > 0.64) in discriminating sepsis from septic shock.

or no control group, so they could not confirm any differences between septic patients and healthy subjects. There is also agreement with clinical studies depicting hyperesistinemia in septic patients compared to controls [6,19–22,33–36] and an association of serum resistin with sepsis severity [6,19,20,35]. However, only three studies have investigated resistin kinetics in sepsis [19–21], showing increased resistin levels at sepsis onset with a subsequent decrease, as well as an association with sepsis severity [20]. None of these studies have demonstrated any association of resistin with mortality.

In our sepsis population, the positive correlation of serum eNampt with leukocytes and neutrophils at sepsis onset and one week after are in line with clinical studies in patients with sepsis [21,22], pneumonia [37], in children with acute infections [10] and in neonatal sepsis [38]. Our study has shown a positive correlation of resistin with IL-10, IL-6 and TNF-α at enrollment, in line with previous studies [19,20,22,35]. Serum eNampt, but not resistin, was found to correlate significantly with both CRP and procalcitonin at enrollment. Only one previous study has shown a positive correlation of serum resistin with CRP and procalcitonin in septic patients [22], while another one did not confirm this finding [20]. Finally, our study revealed for the first time a better discriminative ability of serum eNampt for sepsis and septic shock at admission compared to classic sepsis biomarkers and cytokines.

Table 3
Receiver Operator Characteristic Curve Analysis to determine the optimum cutoff value of significant circulating biomarkers in order to discriminate sepsis from septic shock in 102 patients with sepsis.

Biomarkers	AUC (95% CI)	p value	Sensitivity	Specificity	Youden's index	Cutoff value	Positive Predictive Value	Negative Predictive Value
Resistin	0.69 (0.59–0.80)	0.001	95%	48.3%	0.43	32.41 μg/L	56.3%	93.2%
eNampt	0.83 (0.75–0.91)	< 0.001	75%	75.9%	0.51	76.20 μg/L	68.5%	81.2%
CRP	0.78 (0.68–0.87)	< 0.001	80%	69%	0.49	1,257 nmol/L	64.4%	83.1%
Procalcitonin	0.71 (0.60–0.81)	0.001	60%	82.8%	0.43	4.30 μg/L	70.9%	74.7%
IL-6	0.69 (0.58–0.79)	0.001	70%	62.1%	0.32	24.5 ng/L	56.4%	74.7%
IL-10	0.68 (0.57–0.79)	0.003	60%	82.8%	0.43	5.88 ng/L	70.9%	74.7%
suPAR	0.64 (0.53–0.75)	0.02	75%	58.6%	0.34	11.79 μg/L	55.9%	77%

AUC, Area Under the Curve; CRP, C-reactive protein; IL, interleukin; suPAR, soluble urokinase-type plasminogen activator receptor

Table 4a
Spearman correlations of study variables with circulating eNampt among patients at admission and one week after (N = 102).

Variables	At admission		One week after admission	
	r	p	r	p
BMI	0.160	0.107		
Clinical scoring				
APACHE II	0.460	< 0.001	0.447	< 0.001
SOFA	0.449	< 0.001	0.415	< 0.001
Hematologic parameters				
Hemoglobin	−0.020	0.840	−0.053	0.597
White Blood Cells	0.308	0.002	0.358	< 0.001
Neutrophils	0.276	0.005	0.380	< 0.001
Platelets	−0.018	0.859	−0.342	< 0.001
Biomarkers of organ function				
Albumin	−0.226	0.022	−0.285	0.004
Lactate	0.547	< 0.001	0.402	< 0.001
Creatinine	0.355	< 0.001	0.212	0.032
Metabolic biomarkers				
Total protein	−0.313	0.001	−0.496	< 0.001
Glucose	0.279	0.004	–	–
Insulin	0.566	< 0.001	–	–
HOMA-IR	0.459	< 0.001	–	–
Triglycerides	−0.089	0.432	−0.202	0.089
Total Cholesterol	−0.122	0.275	−0.279	0.017
LDL-Cholesterol	−0.044	0.705	−0.166	0.182
HDL-Cholesterol	−0.082	0.476	−0.220	0.076
Coagulation markers				
PT	0.369	< 0.001	0.180	0.076
INR	0.427	< 0.001	0.215	0.031
aPTT	0.414	< 0.001	0.218	0.029
Fibrinogen	0.064	0.539	−0.09	0.397
Classic biomarkers of sepsis				
CRP	0.428	< 0.001	−0.058	0.563
Procalcitonin	0.248	0.012	0.224	0.024
Adipocytokine				
Resistin	0.510	< 0.001	0.702	< 0.001
Cytokines				
IL-1β	0.097	0.335	−0.095	0.356
IL-6	0.184	0.066	−0.077	0.459
IL-10	0.209	0.039	−0.125	0.232
TNF-α	−0.091	0.366	0.089	0.387
suPAR[b]	0.069	0.495	0.085	0.408

APACHE II, acute physiology and chronic health evaluation score; aPTT, activated Partial Thromboplastin Time; BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IL, interleukin; INR, International Normalized Ratio; LDL, low-density lipoprotein; PT, prothrombin time; SOFA, sequential organ failure assessment score; suPAR, soluble urokinase-type plasminogen activator receptor; TNF-α, tumor necrosis factor alpha

Table 4b
Spearman correlations of study variables with circulating resistin among patients at admission and one week after (N = 102).

Variables	At admission		One week after admission	
	r	p	r	p
BMI	0.039	0.699		
Clinical scoring				
APACHE II	0.274	0.005	0.498	< 0.001
SOFA	0.325	0.001	0.436	< 0.001
Hematologic parameters				
Hemoglobin	−0.113	0.256	−0.091	0.364
White Blood Cells	0.038	0.708	0.379	< 0.001
Neutrophils	0.013	0.893	0.356	< 0.001
Platelets	0.042	0.676	−0.264	0.007
Biomarkers of organ function				
Albumin	−0.083	0.409	−0.245	0.013
Lactate	0.327	0.001	0.343	< 0.001
Creatinine	0.148	0.138	0.228	0.021
Metabolic biomarkers				
Total protein	−0.120	0.229	−0.401	< 0.001
Glucose	0.106	0.289		
Insulin	0.466	< 0.001		
HOMA-IR	0.325	0.001		
Triglycerides	0.157	0.165	−0.131	0.271
Total Cholesterol	−0.115	0.302	−0.165	0.166
LDL-Cholesterol	−0.254	0.027	−0.121	0.332
HDL-Cholesterol	−0.053	0.645	−0.176	0.157
Coagulation markers				
PT	0.244	0.014	0.264	0.015
INR	0.322	0.001	0.271	0.006
aPTT	0.094	0.349	0.108	0.284
Fibrinogen	0.189	0.065	−0.011	0.915
Classic biomarkers of sepsis				
CRP	0.194	0.051	0.028	0.783
Procalcitonin	0.036	0.718	0.245	0.013
Adipocytokine				
eNampt	0.510	< 0.001	0.702	< 0.001
Cytokines				
IL-1β	0.109	0.279	−0.086	0.403
IL-6	0.263	0.008	0.012	0.904
IL-10	0.224	0.026	0.105	0.316
TNF-α	−0.263	0.008	0.001	0.994
suPAR[b]	0.032	0.752	0.146	0.156

APACHE II, acute physiology and chronic health evaluation score; aPTT, activated Partial Thromboplastin Time; BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IL, interleukin; INR, International Normalized Ratio; LDL, low-density lipoprotein; PT, prothrombin time; SOFA, sequential organ failure assessment score; suPAR, soluble urokinase-type plasminogen activator receptor; TNF-α, tumor necrosis factor alpha

Accordingly, there is only one study showing the superiority of eNampt in the diagnosis of neonatal sepsis compared to CRP and procalcitonin [38].

Both eNampt and resistin are proinflammatory adipocytokines associated with both acute and chronic inflammatory states [9–11,31–33,37,38]. Their expression pattern resembles acute-phase

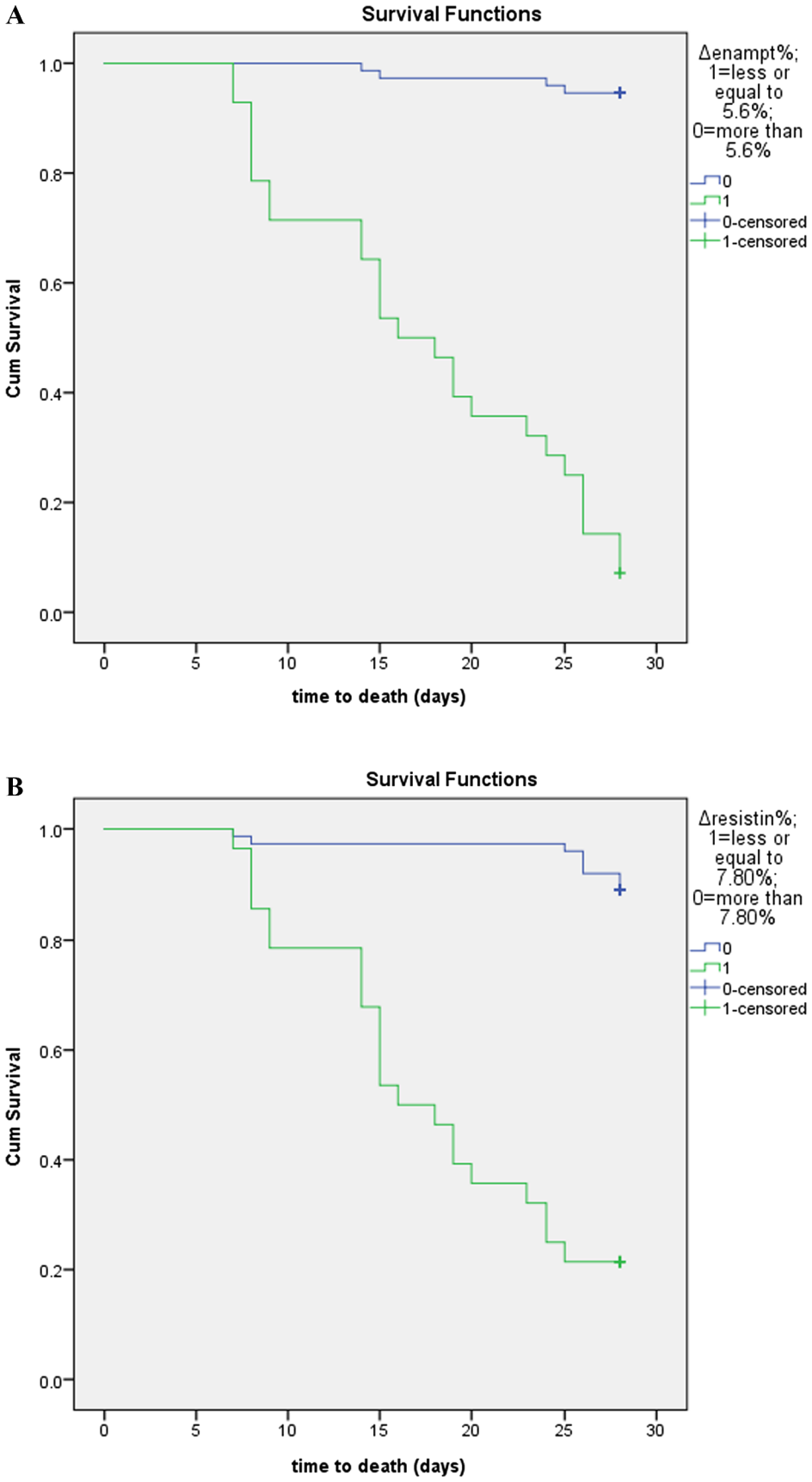

Fig. 4. Kaplan-Meier estimates of mortality in 102 septic patients based on percentage change from baseline serum adipocytokine cutoff values obtained via ROC analysis. A. eNampt (Log rank test: 106.5, $p < 0.001$). B. resistin (Log rank test: 66.5, $p < 0.001$).

Table 5
Multivariate Cox Regression analysis results for the independent laboratory predictors of mortality: circulating resistin, eNampt, C-reactive protein, procalcitonin and IL-6 (all expressed as quartiles) adjusting for age, gender, BMI, HOMA-IR, APACHE II score and presence of septic shock in 102 septic patients.

	b	SE_b	Wald	df	p-value	HR	95% for C.I.
Independent predictors on admission							
Resistin	1.33	0.44	9.24	1	**0.002**	3.78	1.60–8.91
eNampt	1.22	0.33	13.69	1	**< 0.001**	3.40	1.77–6.50
CRP	0.06	0.02	6.16	1	**0.013**	1.06	1.01–1.17
PCT	1.19	0.34	12.1	1	**0.001**	3.30	1.68–6.47
IL-6	0.53	0.24	4.70	1	**0.03**	1.70	1.05–2.74
Independent predictors on day 7							
Resistin	1.49	0.60	6.11	1	**0.013**	4.42	1.36–14.36
eNampt	2.51	0.61	16.77	1	**< 0.001**	12.26	3.69–40.68
PCT	1.51	0.42	13.03	1	**< 0.001**	4.54	1.99–10.33
WBC	−0.29	0.29	1.01	1	0.31	0.74	0.41–1.33
Independent predictors expressed as absolute percentage change (%) from baseline variables							
ΔResistin%	−1.64	0.49	11.32	1	**0.001**	0.19	0.07–0.50
ΔeNampt%	−2.94	0.84	12.09	1	**0.001**	0.05	0.01–0.28
ΔCRP%	−0.43	0.37	1.35	1	0.24	0.65	0.31–1.34
ΔPCT%	−0.33	0.24	1.83	1	0.18	0.72	0.44–1.16
ΔWBC%	−0.09	0.24	0.14	1	0.71	0.91	0.56–1.47

In bold statistical significant results
b, regression coefficient; CI, Confidence Interval; df, degree of freedom; HR, Hazard Ratio; SE_b, standard error of b; CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin; WBC, White Blood Cell

proteins in the setting of acute bacterial infection and sepsis [18–23,31–33,37,38], while they have both been found to increase in chronic inflammation and to correlate positively with disease activity [7,10,12]. The findings of our study are consistent with experimental data regarding the role of eNampt and resistin in innate immune responses and inflammation. Both adipocytokines are upregulated in monocytes exposed to IL-1β, TNF-α, IL-6 and LPS, while -as part of a positive feedback loop- they induce proinflammatory cytokines production. eNampt further activates T-cells, B-cells and monocytes and contributes to prolonged neutrophil survival in sepsis [4,7,8,10,16,17]. Specifically, eNampt expression has been shown to increase in LPS-stimulated neutrophils and neutrophils from critically ill patients with sepsis in whom apoptosis is profoundly delayed [8]. Activated neutrophils represent the main culprit of tissue damage leading to multiple organ dysfunction in sepsis, through the production of enzymes and reactive oxygen species. Thus, delayed neutrophil apoptosis enhance and preserve inflammation. The eNampt action on neutrophil survival in sepsis may be explained by inhibition of caspases 8 and 3 [8] and stimulation of the mitogen-activated protein kinase (MAPK) and the NF-κB signaling pathways [9]. Remarkably, eNampt directly binds and activates TLR-4 in the absence of bacterial infection, inducing directly TLR-4-mediated NF-κB activation, unlike LPS or other inflammatory mediators [39]. Resistin also competes with LPS for binding to TLR-4 and induces the release of IL-1β, IL-6, IL-12 and TNF-α from monocytes and macrophages, through activation of the critical NF-κB pathway [13–15]

Nampt, as a rate-limiting intracellular enzyme in nicotinamide adenine dinucleotide (NAD) biosynthesis, holds a critical role in cell cycle, homeostasis and life-span, through regulation of NAD-consuming enzymes such as sirtuins [5], and on the other hand contributes to the initiation of the respiratory burst generating reactive oxygen species, a key factor in neutrophil antimicrobial defense. Thus, Nampt is an attractive therapeutic target, as its biochemical neutralization has showed promising results in experimental models of sepsis and acute lung injury [40].

This is the first study to investigate the parallel change over time of both eNampt and resistin and its correlation to sepsis outcome. The prospective case-control design along with the careful selection of cases constitutes the main strength of our study. However, there are certain limitations meriting discussion. This is a single center study; therefore, generalization of our results cannot be assumed. However, the study design ensured that all patients received standard care. Our results could not depict possible variations in serum levels over hours or days during the course of sepsis. Although we demonstrated a significant difference between septic patients and healthy controls, the design of the study could not provide serum adipocytokine determinations in our patient population before sepsis onset. There is only one prospective study in 14 postoperative patients that showed a significant increase in plasma resistin after sepsis onset compared to pre-septic levels [23]. Finally, we didn't record clinical data regarding persistent hypotension and vasopressor requirement one week after enrollment. Thus, we didn't report any data on the course of sepsis during the first week (resolution or worsening) as the main outcome of the study was 28-day mortality.

5. Conclusions

We have found that the proinflammatory adipocytokines, eNampt and resistin, are significantly elevated in critically ill septic patients, while their sustained elevation during the first week is independently associated with severity and mortality of sepsis. Thus, eNampt and resistin may represent useful diagnostic and prognostic biomarkers for sepsis, especially in early risk stratification of septic patients. Since the journey of eNampt and resistin's duet in the pathophysiology of sepsis has just begun, more prospective studies are warranted to shed light on their ontological and pathogenetic role in sepsis.

Declaration of interest

None

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References

[1] D.C. Angus, T. van der Poll, Severe sepsis and septic shock, N. Engl. J. Med. 369 (2013) 840–851.
[2] R.P. Dellinger, M.M. Levy, A. Rhodes, D. Annane, H. Gerlach, S.M. Opal, J.E. Sevransky, C.L. Sprung, I.S. Douglas, R. Jaeschke, T.M. Osborn, M.E. Nunnally, S.R. Townsend, K. Reinhart, R.M. Kleinpell, D.C. Angus, C.S. Deutschman, F.R. Machado, G.D. Rubenfeld, S. Webb, R.J. Beale, J.L. Vincent, Moreno R (2013) Surviving Sepsis Campaign: international guidelines for management of severe

sepsis and septic shock, Intensive Care Med. 39 (2) (2012) 165–228.
[3] M. Singer, C.S. Deutschman, C.W. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, R. Bellomo, G.R. Bernard, J.D. Chiche, C.M. Coopersmith, R.S. Hotchkiss, M.M. Levy, J.C. Marshall, G.S. Martin, S.M. Opal, G.D. Rubenfeld, T. van der Poll, J.L. Vincent, D.C. Angus, The third international consensus definitions for sepsis and septic shock (Sepsis-3), JAMA 315 (8) (2016) 801–810.
[4] A. Hillenbrand, M. Weiss, U. Knippschild, A.M. Wolf, M. Huber-Lang, Sepsis-induced adipokine change with regard to insulin resistance, Int. J. Inflam. 2012 (2012) 972368.
[5] M. Dalamaga, G.S. Christodoulatos, C.S. Mantzoros, The role of extracellular and intracellular Nicotinamide phosphoribosyl-transferase in cancer: diagnostic and therapeutic perspectives and challenges, Metabolism 82 (2018) 72–87.
[6] A. Hillenbrand, U. Knippschild, M. Weiss, H. Schrezenmeier, D. Henne-Bruns, M. Huber-Lang, A.M. Wolf, Sepsis induced changes of adipokines and cytokines - septic patients compared to morbidly obese patients, BMC Surg. 10 (2010) 26.
[7] A.R. Moschen, A. Kaser, B. Enrich, B. Mosheimer, M. Theurl, H. Niederegger, H. Tilg, Visfatin, an adipocytokine with proinflammatory and immunomodulating properties, J. Immunol. 178 (3) (2007) 1748–1758.
[8] S.H. Jia, Y. Li, J. Parodo, A. Kapus, L. Fan, O.D. Rotstein, J.C. Marshall, Pre-B cell colony-enhancing factor inhibits neutrophil apoptosis in experimental inflammation and clinical sepsis, J. Clin. Invest. 113 (9) (2004) 1318–1327.
[9] S. Pilz, H. Mangge, B. Obermayer-Pietsch, W. Marz, Visfatin/pre-B-cell colony-enhancing factor: a protein with various suggested functions, J. Endocrinol. Invest 30 (2) (2007) 138–144.
[10] J. Gesing, K. Scheuermann, I.V. Wagner, D. Loffler, D. Friebe, W. Kiess, V. Schuster, A. Körner, NAMPT serum levels are selectively elevated in acute infectious disease and in acute relapse of chronic inflammatory diseases in children, PloS One 12 (8) (2017) e0183027.
[11] S.Q. Ye, B.A. Simon, J.P. Maloney, A. Zambelli-Weiner, L. Gao, A. Grant, R.B. Easley, B.J. McVerry, R.M. Tuder, T. Standiford, R.G. Brower, K.C. Barnes, J.G. Garcia, Pre-B-cell colony-enhancing factor as a potential novel biomarker in acute lung injury, Am. J. Respir. Crit. Care Med. 171 (4) (2005) 361–370.
[12] M. Lehrke, M.P. Reilly, S.C. Millington, N. Iqbal, D.J. Rader, M.A. Lazar, An inflammatory cascade leading to hyperresistinemia in humans, PLoS Med 1 (2) (2004) e45.
[13] A. Tarkowski, J. Bjersing, A. Shestakov, M.I. Bokarewa, Resistin competes with lipopolysaccharide for binding to toll-like receptor 4, J. Cell Mol. Med. 14 (6B) (2010) 1419–1431.
[14] N. Silswal, A.K. Singh, B. Aruna, S. Mukhopadhyay, S. Ghosh, N.Z. Ehtesham, Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappa B-dependent pathway, Biochem. Biophys. Res. Commun. 334 (4) (2005) 1092–1101.
[15] M. Dalamaga, Resistin as a biomarker linking obesity and inflammation to cancer: potential clinical perspectives, Biomark Med. 8 (1) (2014) 107–118.
[16] S.C. Lu, W.Y. Shieh, C.Y. Chen, S.C. Hsu, H.L. Chen, Lipopolysaccharide increases resistin gene expression in vivo and in vitro, FEBS Lett. 530 (1–3) (2002) 158–162.
[17] M. Dalamaga, G. Sotiropoulos, K. Karmaniolas, N. Pelekanos, E. Papadavid, A. Lekka, Serum resistin: a biomarker of breast cancer in postmenopausal women? Association with clinicopathological characteristics, tumor markers, inflammatory and metabolic parameters, Clin. Biochem. 46 (7–8) (2013) 584–590.
[18] M. Filkova, M. Haluzik, S. Gay, L. Senolt, The role of resistin as a regulator of inflammation: implications for various human pathologies, Clin. Immunol. 133 (2) (2009) 157–170.
[19] J. Sunden-Cullberg, T. Nystrom, M.L. Lee, G.E. Mullins, L. Tokics, J. Andersson, A. Norrby-Teglund, C.J. Treutiger, Pronounced elevation of resistin correlates with severity of disease in severe sepsis and septic shock, Crit. Care Med. 35 (6) (2007) 1536–1542.
[20] D.A. Vassiliadi, M. Tzanela, A. Kotanidou, S.E. Orfanos, N. Nikitas, A. Armaganidis, M. Koutsilieris, C. Roussos, S. Tsagarakis, I. Dimopoulou, Serial changes in adiponectin and resistin in critically ill patients with sepsis: Associations with sepsis phase, severity, and circulating cytokine levels, J. Crit. Care 27 (4) (2012) 400–409.
[21] L. Johansson, A. Linner, J. Sunden-Cullberg, A. Haggar, H. Herwald, K. Lore, C.J. Treutiger, A. Norrby-Teglund, Neutrophil-derived hyperresistinemia in severe acute streptococcal infections, J. Immunol. 183 (6) (2009) 4047–4054.
[22] A. Koch, O.A. Gressner, E. Sanson, F. Tacke, C. Trautwein, Serum resistin levels in critically ill patients are associated with inflammation, organ dysfunction and metabolism and may predict survival of non-septic patients, Crit. Care 13 (3) (2009) R95.
[23] A. Hillenbrand, P. Xu, S. Zhou, A. Blatz, M. Weiss, S. Hafner, D. Henne-Bruns, U. Knippschild, Circulating adipokine levels and prognostic value in septic patients, J. Inflamm. (Lond) 13 (1) (2016) 30.
[24] I. Karampela, E. Kandri, G. Antonakos, E. Vogiatzakis, G.S. Christodoulatos, A. Nikolaidou, G. Dimopoulos, A. Armaganidis, M. Dalamaga, Kinetics of circulating fetuin-A may predict mortality independently from adiponectin, high molecular weight adiponectin and prognostic factors in critically ill patients with sepsis: a prospective study, J. Crit. Care 41 (2017) 78–85.
[25] M. Dalamaga, K. Karmaniolas, A. Panagiotou, A. Hsi, J. Chamberland, C. Dimas, A. Lekka, C.S. Mantzoros, Low circulating adiponectin and resistin, but not leptin, levels are associated with multiple myeloma risk: a case-control study, Cancer Causes Control 20 (2) (2009) 193–199.
[26] M. Dalamaga, K. Karmaniolas, E. Papadavid, N. Pelekanos, G. Sotiropoulos, A. Lekka, Hyperresistinemia is associated with postmenopausal breast cancer, Menopause 20 (8) (2013) 845–851.
[27] M. Dalamaga, K. Karmaniolas, G. Sotiropoulos, N. Pelekanos, E. Papadavid, A. Lekka, Could serum visfatin be a potential biomarker for postmenopausal breast cancer? Maturitas 71 (3) (2012) 301–308.
[28] M. Dalamaga, K. Karmaniolas, E. Papadavid, N. Pelekanos, G. Sotiropoulos, A. Lekka, Elevated serum visfatin/nicotinamide phosphoribosyl-transferase levels are associated with risk of postmenopausal breast cancer independently from adiponectin, leptin, and anthropometric and metabolic parameters, Menopause 18 (11) (2011) 1198–1204.
[29] M. Dalamaga, I. Karampela, Fetuin-A to adiponectin ratio is a promising prognostic biomarker in septic critically ill patients, J. Crit. Care 44 (2018) 134–135.
[30] T. Stratigou, M. Dalamaga, G. Antonakos, I. Marinou, E. Vogiatzakis, G.S. Christodoulatos, I. Karampela, A.G. Papavassiliou, Hyperirisinemia is independently associated with subclinical hypothyroidism: correlations with cardiometabolic biomarkers and risk factors, Endocrine 61 (1) (2018) 83–93.
[31] K. Lee, J.W. Huh, C.M. Lim, Y. Koh, S.B. Hong, Clinical role of serum pre-B cell colony-enhancing factor in ventilated patients with sepsis and acute respiratory distress syndrome, Scand. J. Infect. Dis. 45 (10) (2013) 760–765.
[32] K.A. Lee, M.N. Gong, Pre-B-cell colony-enhancing factor and its clinical correlates with acute lung injury and sepsis, Chest 140 (2) (2011) 382–390.
[33] S.P. Macdonald, S.F. Stone, C.L. Neil, P.E. van Eeden, D.M. Fatovich, G. Arendts, S.G. Brown, Sustained elevation of resistin, NGAL and IL-8 are associated with severe sepsis/septic shock in the emergency department, PloS One 9 (10) (2014) e110678.
[34] J. Snall, A. Linner, J. Uhlmann, N. Siemens, H. Ibold, M. Janos, A. Linder, B. Kreikemeyer, H. Herwald, L. Johansson, A. Norrby-Teglund, Differential neutrophil responses to bacterial stimuli: streptococcal strains are potent inducers of heparin-binding protein and resistin-release, Sci. Rep. 6 (2016) 21288.
[35] S.P.J. Macdonald, E. Bosio, C. Neil, G. Arendts, S. Burrows, L. Smart, S.G.A. Brown, D.M. Fatovich, Resistin and NGAL are associated with inflammatory response, endothelial activation and clinical outcomes in sepsis, Inflamm. Res. 66 (7) (2017) 611–619.
[36] A. Bonavia, L. Miller, J.A. Kellum, K. Singbartl, Hemoadsorption corrects hyperresistinemia and restores anti-bacterial neutrophil function, Intensive Care Med. Exp. 5 (1) (2017) 36.
[37] W. Hu, C.W. Liu, J. Su, J. Lu, Y. Zhu, B.W. Liu, Elevated plasma visfatin concentrations in patients with community-acquired pneumonia, Peptides 43 (2013) 8–12.
[38] F. Cekmez, F.E. Canpolat, M. Cetinkaya, S. Aydinoz, G. Aydemir, F. Karademir, O.M. Ipcioglu, S.Ü. Sarici, Diagnostic value of resistin and visfatin, in comparison with C-reactive protein, procalcitonin and interleukin-6 in neonatal sepsis, Eur. Cytokine Netw. 22 (2) (2011) 113–117.
[39] S.M. Camp, E. Ceco, C.L. Evenoski, S.M. Danilov, T. Zhou, E.T. Chiang, L. Moreno-Vinasco, B. Mapes, J. Zhao, G. Gursoy, M.E. Brown, D.M. Adyshev, S.S. Siddiqui, H. Quijada, S. Sammani, E. Letsiou, L. Saadat, M. Yousef, T. Wang, J. Liang, J.G. Garcia, Unique toll-like receptor 4 activation by NAMPT/PBEF induces NFκB signaling and inflammatory lung injury, Sci. Rep. 14 (5) (2015) 13135.
[40] L. Moreno-Vinasco, H. Quijada, S. Sammani, J. Siegler, E. Letsiou, R. Deaton, L. Saadat, R.S. Zaidi, J. Messana, P.H. Gann, R.F. Machado, W. Ma, S.M. Camp, T. Wang, J.G. Garcia, Nicotinamide phosphoribosyltransferase inhibitor is a novel therapeutic candidate in murine models of inflammatory lung injury, Am. J. Respir. Cell Mol. Biol. 51 (2) (2014) 223–228.