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Divergent temporal trajectories of adiponectin and leptin in critically ill patients with COVID-19-associated acute respiratory distress syndrome

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Informed consent: written informed consent was obtained from all patients or, when patients were unable to provide consent due to their clinical condition, from their legally authorized representatives.

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Abstract

Adipokines play an important role in immunometabolic regulation and systemic inflammation, processes profoundly disturbed in COVID-19. Leptin and adiponectin have attracted particular interest because of their opposing biological effects. However, most studies have relied on single time-point measurements, and data on serial adipokine dynamics in critically ill patients with COVID-19–associated acute respiratory distress syndrome (ARDS) remain limited. This study aimed to evaluate circulating leptin and adiponectin concentrations and their temporal changes during the first week of intensive care unit (ICU) treatment. This single-center prospective observational study included 75 adults with COVID-19–associated ARDS admitted to the medical ICU (MICU). Serum leptin and adiponectin concentrations were measured on day 1 and day 7 using enzyme-linked immunosorbent assays. Clinical data, including respiratory support, vasopressor use, comorbidities, and 28-day survival, were prospectively collected. The overall 28-day mortality was 38.7%. Leptin concentrations did not significantly change between day 1 and day 7 in any subgroup. In contrast, adiponectin demonstrated significant temporal changes. Among non-survivors, adiponectin levels decreased markedly during the first week of MICU treatment ($p<0.001$), whereas no significant change was observed in survivors. Similar declines were observed in patients requiring invasive mechanical ventilation and vasopressor therapy, while patients managed without these interventions showed increasing adiponectin concentrations. The leptin-to-adiponectin ratio showed a trend toward higher values in non-survivors but did not reach statistical significance. In COVID-19–associated ARDS patients, adiponectin demonstrated dynamic changes associated with clinical deterioration, whereas leptin remained relatively stable. These findings suggest that serial adiponectin measurements may have potential for monitoring short-term disease progression in critically ill patients and warrant confirmation in larger prospective studies.

Key words: COVID-19-associated ARDS, adiponectin, leptin, critical illness.

Introduction

Adipose tissue is increasingly recognized as an active endocrine and immunometabolic organ rather than merely a reservoir for energy storage. It secretes numerous bioactive mediators, including adipokines such as leptin and adiponectin, which participate in the regulation of metabolic homeostasis, inflammation, immune responses, and vascular function [1,2]. Because of these pleiotropic biological effects, adipokines have attracted growing interest in conditions characterized by systemic inflammation and metabolic dysregulation, including critical illness. Severe coronavirus disease 2019 (COVID-19) is associated with profound immune activation, dysregulated inflammatory responses, endothelial injury, and metabolic disturbances. These pathophysiological processes contribute to the development of acute respiratory distress syndrome (ARDS) and multiple organ dysfunction in critically ill patients [3]. Given their immunomodulatory and metabolic roles, adipokines have been proposed as potential mediators linking metabolic status with the host inflammatory response during severe infection [4]. Leptin exerts predominantly pro-inflammatory effects and plays an important role in both innate and adaptive immune responses, in addition to its established function in appetite regulation and energy metabolism [5,6]. In contrast, adiponectin generally exhibits anti-inflammatory and insulin-sensitizing properties, and circulating levels are typically reduced in obesity and metabolic dysfunction [7]. These contrasting biological effects have raised interest in the potential role of leptin and adiponectin as markers of immunometabolic dysregulation in inflammatory diseases. Several studies have reported altered adipokine profiles in patients with COVID-19, including increased leptin concentrations and reduced adiponectin levels in more severe disease phenotypes [8]. However, the available evidence remains heterogeneous, and most studies have relied on single-time-point measurements or mixed cohorts of hospitalized patients with varying disease severity. Prospective data examining serial changes in leptin and adiponectin in critically ill patients with COVID-19-associated ARDS remain scarce, and the relationship between early adipokine trajectories and clinically relevant outcomes has not been fully clarified [9,10]. Understanding the temporal behavior of adipokines in critical illness may provide additional insight into the immunometabolic mechanisms underlying severe COVID-19 and may help identify biomarkers associated with disease progression. Therefore, the present study aimed to evaluate circulating leptin and adiponectin concentrations in critically ill patients with severe COVID-19–associated ARDS and to characterize their temporal trajectories during the first week of MICU treatment. We further explored whether dynamic changes in these adipokines were

associated with clinically relevant outcomes, including survival, need for invasive mechanical ventilation, presence of comorbidities, and vasopressor use. ~~and renal replacement therapy~~. We hypothesized that temporal trajectories of circulating adipokines, particularly adiponectin, may be associated with disease severity and clinical outcomes in critically ill patients with COVID-19.

Materials and Methods

Study design and setting

This was a single-center prospective observational study conducted in the multidisciplinary Medical Intensive Care Unit (MICU) of the University Clinical Center of the Republic of Srpska in Banja Luka, Bosnia and Herzegovina. The study was performed between late 2020 and the first half of 2021 and included critically ill adult patients admitted with severe COVID-19 pneumonia and respiratory failure consistent with COVID-19–associated ARDS. The study protocol was approved by the Ethics Committee of the University Clinical Center of the Republic of Srpska (No. 01-19-570-2/20) and the Ethics Committee for Research on Humans and Biological Material of the Faculty of Medicine, University of Banja Luka (No. 18/4.139/21). Written informed consent was obtained from all patients or, when patients were unable to provide consent due to their clinical condition, from their legally authorized representatives. The study was conducted in accordance with the principles of the Declaration of Helsinki. The present analysis represents a predefined biomarker sub-analysis of a broader prospective cohort investigating pathophysiological mechanisms and biomarkers in critically ill COVID-19–associated ARDS.

Study population

A total of 99 patients of both sexes with severe COVID-19–associated ARDS requiring treatment in the MICU were initially enrolled in the study. Due to the requirement for paired measurements on day 1 and day 7, patients who died before day 7 or had missing follow-up samples were excluded from the longitudinal analysis. Consequently, 75 patients were included in the final analysis. Eligible patients were aged 18 years or older, had microbiologically confirmed SARS-CoV-2 infection detected by polymerase chain reaction (PCR) from nasopharyngeal, throat, or tracheal aspirate samples, and had COVID-19–associated ARDS requiring advanced respiratory support, including high-flow nasal oxygen, non-invasive mechanical ventilation (NIV), or invasive mechanical ventilation (IMV).

These patients had moderate to severe ARDS according to the Berlin definition, with a PaO_2/FiO_2 ratio ≤ 200 mmHg at MICU admission. Patients were excluded if they were pregnant or breastfeeding, ~~or~~ if SARS-CoV-2 infection had not been microbiologically confirmed, or the absence of day 7 measurement. Patients who died before day 7 of hospitalization were excluded from paired longitudinal analyses, as the study design required two sampling time points (day 1 and day 7) to assess adipokine dynamics. Patients were also excluded if participation in the study was withdrawn by the patient or their legally authorized representative. All patients were followed for 28 days after inclusion, and the clinical outcome was recorded as survival or death.

Clinical data collection

Clinical and demographic data were obtained from paper medical records and the electronic hospital information system while ensuring patient confidentiality. Baseline characteristics recorded at the time of MICU admission included age, sex, body mass index (BMI), presence of comorbidities, and regular medication use. In addition, the time interval from symptom onset to MICU admission was documented, together with the source of MICU admission, including the emergency department, hospital ward, or transfer from a regional hospital. The severity of illness during the first 24 hours of MICU admission was assessed using the Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, which were calculated according to standard definitions. During MICU stay, additional clinical variables were recorded, including MICU length of stay, type of respiratory support, duration of mechanical ventilation, and vasopressor use. For the purpose of the present analysis, circulating leptin and adiponectin concentrations were evaluated in relation to clinically relevant variables, including survival status, presence of comorbidities, requirement for invasive mechanical ventilation, and vasopressor use.

Blood sampling and adipokine measurements

Venous blood samples were obtained on day 1 and day 7 of MICU treatment, either from a central venous catheter or from a peripheral vein under aseptic conditions. After collection, samples were centrifuged within 30 minutes to obtain serum, and serum aliquots were stored at −80 °C until analysis. Serum concentrations of leptin and adiponectin were measured using enzyme-linked immunosorbent assay (ELISA). Commercial ELISA kits provided by Euroimmun (Germany) were used, and all measurements were performed on the Euroimmun I2 automated

analyzer in accordance with the manufacturer's instructions. All samples were analyzed in duplicate and processed in the same analytical batch to minimize potential inter-assay variability.

Outcomes

The primary objective of this analysis was to evaluate circulating leptin and adiponectin concentrations in critically ill patients with severe COVID-19-associated ARDS and to assess their temporal changes between day 1 and day 7 of MICU treatment. In addition, secondary analyses explored the association between adipokine concentrations and clinically relevant outcomes, including 28-day survival, requirement for invasive mechanical ventilation, presence of comorbidities, and vasopressor use.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Body mass index (BMI) data were available for 69 of the 75 patients; therefore, analyses involving BMI were performed on an available-case basis. Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on their distribution, whereas categorical variables are expressed as counts and percentages. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Comparisons between two independent groups were performed using Student's t-test for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Paired changes in leptin and adiponectin concentrations between day 1 and day 7 were analyzed using the Wilcoxon signed-rank test within predefined clinical subgroups. Given the exploratory nature of the subgroup analyses, no adjustment for multiple comparisons was applied. All tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 75 critically ill adults with severe COVID-19–associated ARDS were included in the study, with an overall 28-day mortality of 38.7%. No statistically significant differences were observed between survivors and nonsurvivors regarding sex distribution ($p = 0.642$) or BMI

categories (p = 0.852). Most patients were male (72%), and the median age of the cohort was 58 years (IQR 18). Both leptin and adiponectin concentrations were significantly higher in female patients compared with males (p < 0.001 for both). Adiponectin levels differed significantly according to BMI, with lower concentrations observed in patients with BMI ≥ 30 kg/m² compared with those with BMI < 30 kg/m² (6.16 vs 8.72 μg/mL, p = 0.004). In contrast, leptin concentrations did not significantly differ according to BMI (p = 0.118). The most common comorbidities were arterial hypertension (49.3%) and diabetes mellitus (16%). Hypertension was not associated with differences in baseline adipokine concentrations. Patients with diabetes tended to have lower adiponectin concentrations compared with those without diabetes, although this difference did not reach statistical significance (p = 0.061). Baseline demographic and adipokine characteristics are summarized in Tables 1 and 2.

Clinical characteristics

Approximately half of the patients (57.3%) were transferred to the MICU from the regular COVID-19 ward. The mean time from symptom onset to MICU admission was 9.65 ± 4.13 days. The median MICU length of stay was 12 days and was significantly longer in non-survivors compared with survivors (13 vs 9.5 days, p = 0.006). Invasive mechanical ventilation (IMV) was required in 50.7% of patients, whereas 49.3% received non-invasive respiratory support. All non-survivors required invasive mechanical ventilation, whereas the majority of survivors were managed with non-invasive ventilation (p < 0.001). The duration of non-invasive ventilation was longer in survivors compared with non-survivors (7.5 vs 4 days, p = 0.002). Vasopressor therapy was required in 49.3% of patients and was observed exclusively in the non-survivor group (p < 0.001). However, the duration of vasopressor therapy did not significantly differ between survivors and non-survivors. Clinical characteristics of the study population are presented in Table 3.

Temporal changes in adipokine concentrations

Temporal changes in circulating adipokine concentrations between day 1 and day 7 of MICU treatment are presented in Table 4. Leptin concentrations did not significantly change over time in any of the analyzed clinical subgroups, including survival status, type of mechanical ventilation, presence of comorbidities, or vasopressor use. In contrast, adiponectin concentrations demonstrated significant temporal changes in several clinically relevant subgroups. Among non-survivors, adiponectin levels significantly decreased between day 1

and day 7 of MICU treatment (8.38 vs 4.83 µg/mL, $p < 0.001$), whereas no significant change was observed among survivors. A similar pattern was observed in relation to respiratory support. Patients requiring invasive mechanical ventilation exhibited a significant decrease in adiponectin concentrations over time ($p < 0.001$), whereas patients treated with non-invasive ventilation demonstrated a significant increase in adiponectin levels between day 1 and day 7 ($p = 0.044$). In patients with comorbidities, adiponectin concentrations also decreased during MICU treatment ($p = 0.006$), while no significant temporal change was observed in patients without comorbidities. Adiponectin dynamics also differed according to vasopressor use. Patients requiring vasopressor therapy demonstrated a significant decrease in adiponectin concentrations over time ($p < 0.001$), whereas patients not receiving vasopressors showed a significant increase between day 1 and day 7 ($p = 0.021$).

Leptin-to-adiponectin ratio

The leptin-to-adiponectin ratio did not significantly change between day 1 and day 7 of MICU treatment in either survivors or non-survivors. As illustrated in Figures 1 and 2, a slight decrease in the ratio was observed among survivors, whereas non-survivors showed an increase over time; however, this trend did not reach statistical significance ($p = 0.081$).

Discussion

In this prospective study of critically ill patients with severe COVID-19-associated ARDS, the main finding was that adiponectin, rather than leptin, showed clinically relevant temporal changes during the first week of MICU treatment. While leptin concentrations remained relatively stable across the analysed subgroups, adiponectin levels declined significantly in patients with an unfavourable clinical course, including non-survivors, patients requiring invasive mechanical ventilation, those with comorbidities, and those receiving vasopressor support. In contrast, adiponectin increased over time in patients managed without vasopressors and in those receiving non-invasive respiratory support. These findings suggest that serial adiponectin measurements may better reflect short-term disease evolution in severe COVID-19-associated ARDS than leptin alone. The relative stability of leptin in our cohort is noteworthy. Leptin is a pleiotropic adipokine with predominantly pro-inflammatory and immunomodulatory effects, and elevated circulating leptin has been reported in COVID-19-associated ARDS and in ICU patients compared with controls in some prior studies. However, published data remain inconsistent, with other cohorts showing weaker or no clear

associations with clinical outcomes after accounting for age, sex, BMI, or treatment-related confounding [11-13]. Our results align more closely with studies suggesting that circulating leptin may be influenced more strongly by baseline metabolic phenotype than by short-term progression of critical illness [14]. In this context, leptin may reflect constitutional host characteristics, including adiposity and endocrine status, rather than dynamic deterioration during MICU treatment. By contrast, the adiponectin findings in our study point to a potentially more informative role of this adipokine in COVID-19-associated ARDS. Adiponectin is generally regarded as an anti-inflammatory, insulin-sensitizing, and vasculoprotective adipokine, and lower circulating levels have been linked to metabolic dysfunction and adverse cardiometabolic states [15,16]. Previous COVID-19 studies have reported heterogeneous results, but several have described lower adiponectin concentrations in severe or critical illness, whereas others found no clear association with mortality within already severe cohorts [17,18]. Our data extend this literature by showing that the trajectory of adiponectin may be more informative than a single measurement. The significant decline observed in non-survivors and in patients requiring invasive organ support is consistent with the concept that falling adiponectin may accompany worsening immunometabolic dysregulation, endothelial dysfunction, and circulatory failure in critical COVID-19. The subgroup analyses should be considered exploratory, particularly given the absence of correction for multiple comparisons. Although our observational design does not allow causal inference, these temporal patterns support the hypothesis that adiponectin may serve as a dynamic marker of disease severity. However, these findings should be interpreted in the context of the treatments administered during MICU stay. All patients received corticosteroid and antibiotic therapy, and a subset received tocilizumab during ICU stay. Although the distribution of these therapies was not the primary focus of the study, their potential influence on inflammatory and metabolic pathways, including adipokine levels, cannot be excluded. Patients requiring invasive mechanical ventilation and vasopressor therapy demonstrated a clear decline in adiponectin over time, whereas patients managed with non-invasive ventilation or without vasopressors showed the opposite pattern. This is clinically relevant because the need for invasive respiratory and hemodynamic support generally reflects more advanced organ dysfunction. But, the subgroup findings in patients requiring invasive mechanical ventilation or vasopressor support should be interpreted with caution, as these groups substantially overlapped with the non-survivor cohort, limiting the ability to distinguish the independent effects of organ support from those of mortality. A falling adiponectin signal may therefore track with worsening systemic illness

rather than simply with the presence of SARS-CoV-2 infection itself. This interpretation is also biologically plausible given the known links between adiponectin, endothelial homeostasis, insulin sensitivity, and inflammatory regulation, all of which are profoundly disturbed in COVID-19-associated ARDS. Sex- and BMI-related differences should also be considered when interpreting adipokine data. In our cohort, both leptin and adiponectin were higher in women, while adiponectin was lower in patients with BMI $\geq$ 30 kg/m^2. These findings are in line with the established biology of adipokines and with prior COVID-19 cohorts showing that leptin and adiponectin are strongly influenced by host metabolic characteristics, particularly sex and adiposity [19-21]. This has two implications. First, adipokine concentrations should not be interpreted in isolation from patient phenotype. Second, serial within-patient changes may be more informative than isolated baseline values when evaluating their relationship with disease progression in the ICU. The leptin-to-adiponectin ratio showed a directional pattern that is biologically interesting but should be interpreted cautiously. In our study, the ratio decreased slightly in survivors and increased in non-survivors, yet this difference did not reach statistical significance. Previous studies have suggested that the adiponectin-to-leptin or leptin-to-adiponectin balance may reflect inflammatory burden or adipose tissue dysfunction in COVID-19 [22-23], but those findings have largely come from mixed-severity cohorts and single-time-point analyses. In our critically ill cohort, the observed trend may indicate an unfavourable shift toward a more pro-inflammatory adipokine profile in patients with worse outcomes; however, the current data are insufficient to support a definitive prognostic role for this ratio. Although SOFA and APACHE II scores did not differ significantly between survivors and non-survivors at ICU admission, this may reflect the relatively homogeneous severity of illness in our cohort and the limited sample size. Moreover, these scores represent baseline disease severity, whereas the subsequent need for invasive organ support reflects the clinical course during MICU stay.

Our study has several limitations. First, patients who died before day 7 were excluded from the paired longitudinal analysis due to the absence of a day 7 sample. Consequently, the analysis of serial changes was restricted to patients who survived at least one week, which may have introduced survivor bias and may have attenuated associations with the most severe early trajectories. Second, it was conducted at a single centre with a relatively modest sample size, which limits generalizability and may have reduced statistical power for some subgroup analyses. Third, only two time points were available, precluding a more granular assessment of adipokine kinetics during critical illness. Fourth, the observational design does not allow

conclusions regarding causality, and we did not perform multivariable modelling to determine whether adipokine changes were independent of other markers of disease severity. Fifth, the lack of adjustment for potential treatment-related confounders: all patients received corticosteroid and antibiotic therapy, and a subset received tocilizumab, which may have influenced inflammatory and metabolic pathways, including adipokine levels. Sixth, the absence of a non-COVID critically ill comparator group limits interpretation regarding whether the observed adipokine dynamics are specific to COVID-19 or reflect critical illness more broadly. Finally, although leptin and adiponectin concentrations in the present study were measured using ELISA assays performed on an automated analyzer, these assays are not routinely available or fully automated in many clinical laboratories. This may limit assay standardization, turnaround time, and the feasibility of frequent serial measurements in critically ill patients. Furthermore, the clinical utility and optimal interpretation of leptin and adiponectin measurements in critical illness have not yet been established and require further validation before their routine clinical implementation. Despite these limitations, the prospective design and repeated sampling in an exclusively critically ill cohort represent important strengths.

Conclusions

In conclusion, our findings suggest that serial adiponectin measurements are associated with early clinical trajectories in critically ill patients with COVID-19. Declining adiponectin concentrations were consistently observed in patients with more severe disease courses, including non-survival, invasive mechanical ventilation, and vasopressor requirement. In contrast, leptin remained relatively stable over time. These findings are exploratory and hypothesis-generating, and they support further investigation into the role of adiponectin in the immunometabolic response to critical illness.

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Table 1. Baseline characteristics and circulating adipokine concentrations in critically ill patients with COVID-19.

Variable	All (n= 75)	p
Sex, n (%)		
Male	54 (72)	NA
Female	21 (28)	
Age, years, median (IQR)		
Male	58 (18)	**0.021**
Female	65 (12)	
Leptin (ng/mL), median (IQR)		
Male	9.85 (11.78)	**<0.001**
Female	19.00 (41.66)	
Adiponectin (µg/mL), median (IQR)		
Male	7.70 (5.69)	**<0.001**
Female	11.70 (10.87)	
Leptin at admission by BMI, median (IQR)		
BMI <30 **kg/m²**	12.42 (12.52)	0.118
BMI ≥30 **kg/m²**	16.29 (14.47)	
Adiponectin at admission by BMI, median (IQR)		
BMI <30 **kg/m²**	8.72 (4.56)	**0.004**
BMI ≥30 **kg/m²**	6.16 (4.08)	
Leptin by comorbidities, median (IQR)		
No comorbidities	9.00 (11.95)	0.267
≥1 comorbidity	14.27 (14.18)	
Adiponectin by comorbidities, median (IQR)		
No comorbidities	7.96 (4.08)	0.914
≥1 comorbidity	7.70 (4.98)	
Leptin by hypertension, median (IQR)		
Yes	14.33 (15.83)	0.156
No	11.31 (13.48)	
Adiponectin by hypertension, median (IQR)		
Yes	7.21 (5.10)	0.428
No	8.09 (4.04)	
Leptin by diabetes, median (IQR)		
Yes	17.48 (39.72)	0.343
No	12.47 (12.12)	
Adiponectin by diabetes, median (IQR)		
Yes	6.62 (4.12)	0.061
No	8.06 (4.59)	

BMI, body mass index; IQR, interquartil range; statisticaly significant p< 0.05.

Table 2. Comparison of sex distribution and BMI categories between survivors and nonsurvivors.

Variable	All (n= 75)	Survivors (n= 46)	Nonsurvivors (n= 29)	p- value
Sex, n (%)				
Male, n (%)	54 (72)	34 (63)	20 (37)	0.642
Female, n (%)	21 (28)	12 (57.10)	9 (42.90)	
BMI, kg/m², n (%) (available data, n=69)				
BMI < 30	35	21 (60)	14 (40)	0.852
BMI ≥ 30	34	24 (70.60)	10 (29.40)	
Comorbidities, n (%)				
Hypertension	37 (49.33)	22 (47.83)	15 (51.72)	0.742
Diabetes	12 (16)	6 (13.04)	6 (20.69)	0.519
Cardiomyopathy	5 (6.70)	3 (6.50)	2 (6.90)	0.949
COPD	5 (6.70)	4 (8.70)	1 (3.45)	0.643

BMI, body mass index; COPD, Chronic Obstructive Pulmonary Disease; statisticaly significant p< 0.05; statisticaly significant p< 0.05; *BMI data were available for 69 patients.

Table 3. Clinical characteristics and outcomes of critically ill patients with COVID-19.

Variable	All (n=75)	Survivors (n=46)	Non-survivors (n=29)	*p*-value
Admission source, n (%)				
Emergency department	26 (34.70)	16 (34.80)	10 (34.50%)	0.834
Hospital ward	43 (57.30)	27 (58.70)	16 (55.20)	
Regional hospital	6 (8.00)	3 (6.50)	3 (10.30)	
Time from symptom onset to MICU admission, days (mean ± SD)	9.65 ± 4.13	9.57 ± 3.28	9.79 ± 3.76	0.818
SOFA score, median (IQR)	4 (2)	4 (1)	5 (4)	0.197
APACHE II score, median (IQR)	10 (7)	9.5 (6)	12 (5)	0.098
Treatment modalities during MICU stay, n (%)				
Antibiotic therapy	75 (100)	46 (100)	29 (100)	1.000
Corticosteroid therapy	75 (100)	46 (100)	29 (100)	1.000
Toclizumab	16 (21.30)	12 (26.10)	4 (13.80)	0.256
MICU length of stay, days, median (IQR)	12 (9)	9.5 (8.25)	13 (7.5)	**0.006**
Mechanical ventilation,n (%)				
Invasive mechanical ventilation (IMV)	38 (50.70)	9 (19.60)	29 (100)	**<0.001**
Non-invasive ventilation (NIV)	37 (49.30)	37 (80.40)	0	
Duration of mechanical ventilation, days				
IMV (mean ± SD)	12.43 ± 5.97	14.56 ± 5.48	11.75 ± 6.06	0.225
NIV, median (IQR)	6 (4.5)	7.5 (5.75)	4 (4)	**0.002**
Vasopressor therapy				
Vasopressor use, n (%)	37 (49.30)	8 (17.40)	29 (100)	**<0.001**
Vasopressor duration, days, median (IQR)	5 (3)	4.5 (3)	5 (3.75)	0.288

MICU, medical intensive care unit; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; SD, standard deviation; IQR, interquartile range.

Table 4. Temporal changes in circulating adipokine concentrations between day 1 and day 7 of MICU treatment.

Variable	Leptin Day 1	Leptin Day 7	p	Adiponectin Day 1	Adiponectin Day 7	p
Outcome, median (IQR)						
Survivors (n=46)	13.74 (16.62)	8.39 (12.06)	0.315	7.35 (4.62)	8.33 (5.20)	0.288
Non-survivors (n=29)	10.76 (11.66)	10.29 (13.95)	0.830	8.38 (4.59)	4.83 (3.69)	**<0.001**
Mechanical ventilation, median (IQR)						
IMV (n=38)	11.25 (10.34)	8.38 (10.57)	0.483	8.07 (4.95)	4.91 (3.83)	<0.001
NIV (n=37)	14.27 (18.85)	9.15 (13.94)	0.493	7.35 (4.58)	8.83 (6.04)	**0.044**
Comorbidities, median (IQR)						
≥1 comorbidity (n=54)	14.27 (14.18)	8.41 (10.90)	0.161	7.67 (4.85)	6.35 (5.06)	**0.006**
None (n=21)	9.02 (11.95)	9.22 (20.84)	0.605	7.96 (4.09)	7.68 (4.71)	0.796
Vasopressor therapy, median (IQR)						
Yes (n=37)	11.43 (10.95)	8.38 (11.11)	0.405	8.22 (4.61)	5.29 (4.25)	**<0.001**
No (n=38)	13.75 (17.77)	9.15 (13.60)	0.624	7.21 (3.93)	8.43 (6.14)	**0.021**

IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; IQR, interquartil range; statisticaly significant p< 0.05.

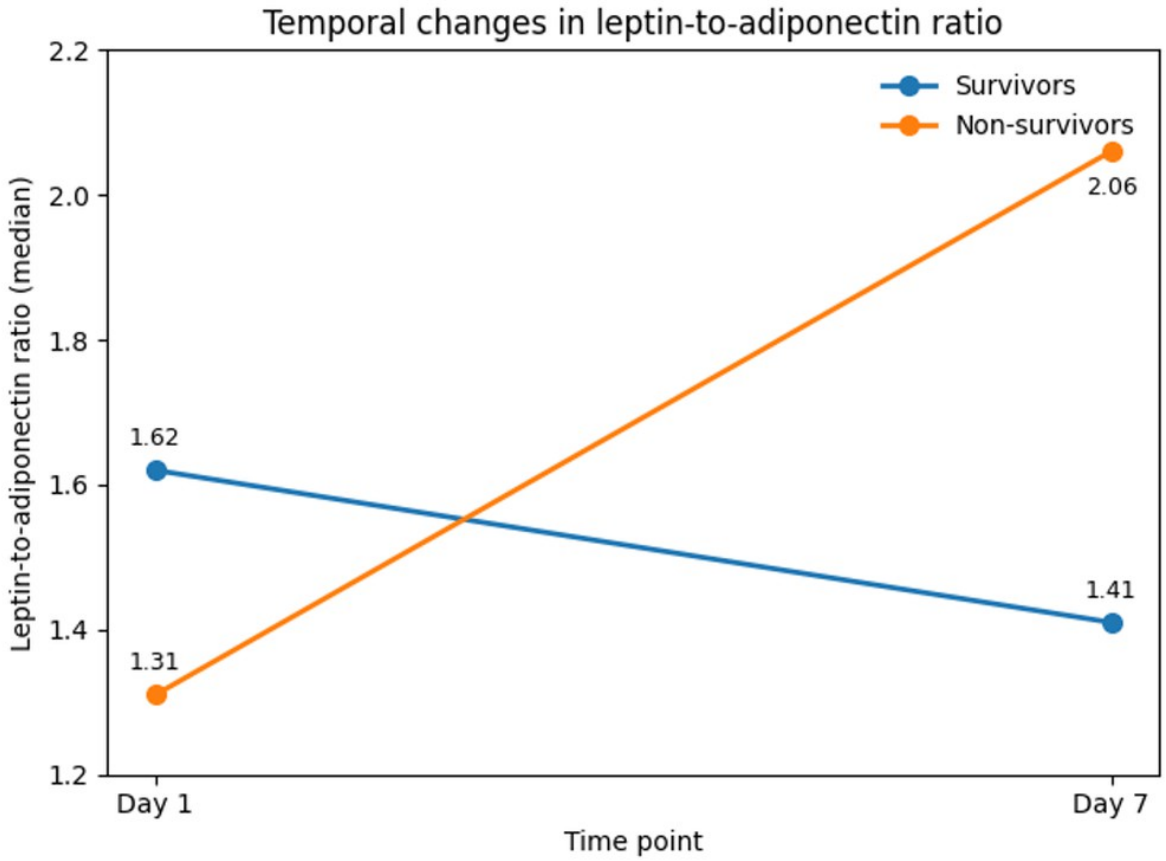

Figure 1. Temporal changes in the leptin-to-adiponectin ratio between day 1 and day 7 according to survival status. Median values are shown for survivors and non-survivors.

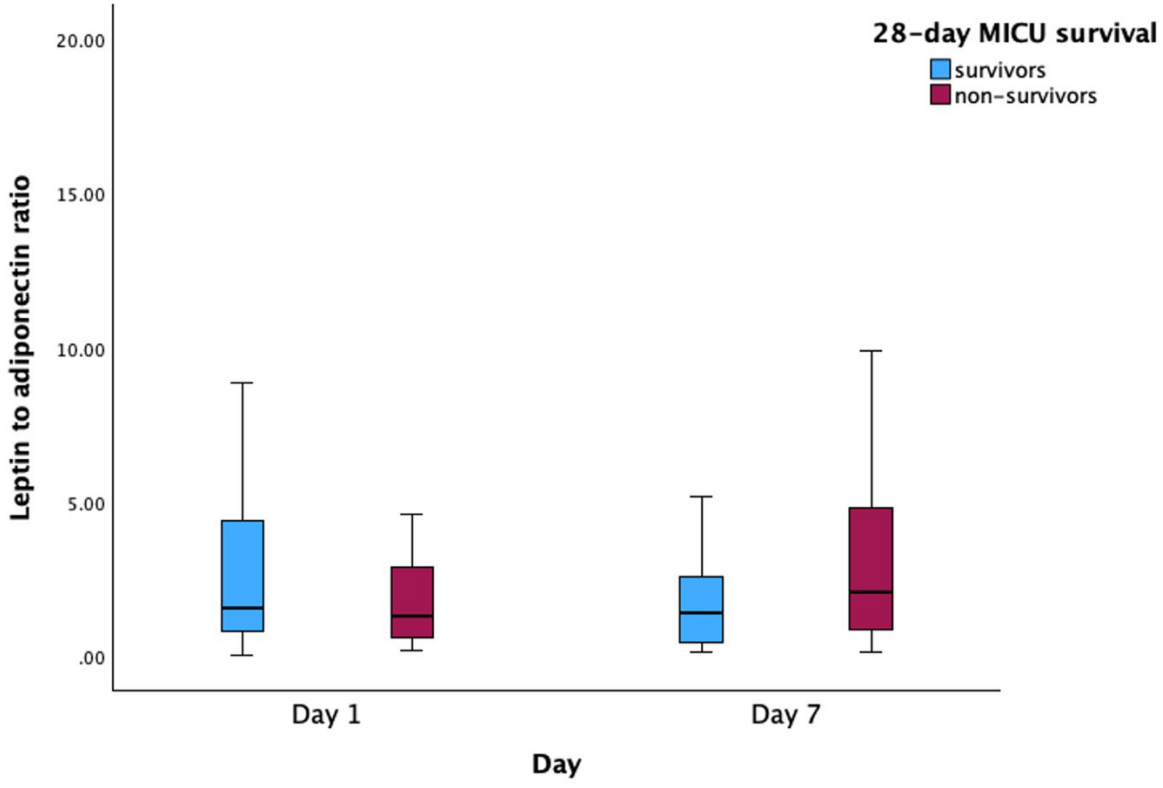

Figure 2. Box plots of the leptin-to-adiponectin ratio on days 1 and 7 according to 28-day survival.