Egyptian Journal of Medical Research

Print ISSN: 2682-4396 / Online ISSN: 2682-440X

Original article

Diagnostic and Prognostic Value of Serum Leptin in Sepsis

Mohamed B. El-Kholy, MD[1], Ahmed M. Sayed, M.B.B.Ch[1], Sameh K. Al-Maraghi, MD[1], Khaled M. Taema, MD[2], And M. Sayed Mohamed, M.D[1].

[1]*Critical care department, Faculty of Medicine, Beni Suef University, Egypt.*

[2]*Critical care department, Faculty of Medicine, Cairo University, Egypt.*

Article Info

Article history:

Received 21 April 2024

Accepted 22 July 2024

Corresponding Author:

M. Sayed Mohamed

mohamed_sayedicu@yahoo.com

Keywords

leptin,

sepsis,

biomarker

Abstract

Background: One of the biggest global health issues and the main cause of intensive care unit (ICU) admissions is sepsis. Biomarkers can have a very vital role in sepsis diagnosis. The 16 kDa, 167-amino acid peptide leptin is mainly produced by adipocytes and has a role in controlling energy balance by telling the brain adipose tissue volume in the body, which in turn controls how much food is consumed and how much energy is used. Leptin is also a cytokine that is involved in cytokine crosstalk and cell-mediated immunity. According to earlier researchs, sepsis patients' leptin level is elevated when compared to controls. **Objective:** Our study aimed to test the validity of serum leptin as a biomarker for sepsis diagnosis and to correlate between the level of leptin and sepsis prognosis and mortality.

Methods: Twenty five critically ill patients diagnosed with sepsis were included in our study, ten healthy volunteers as a control group. The patients were admitted to the critical care department in Beni-Suef university hospital in the period from October 2023 to February 2024.Serum samples were collected from the studied

patients on admission day (day 0), 2nd day of admission (day 2) and 5th day of admission (day 5), and only once in control group to correlate between leptin levels in patients and control group and to find the correlation between leptin and mortality. **Results:** Our study showed that leptin levels showed strong positive correlation with body mass index (BMI). No significant correlation was found between leptin in the studied group and control group on admission (day 0) while there was a highly significant correlation on day 2 and day 5. There was no significant difference in leptin levels between sepsis and septic shock patient on day 0, day 2 and day 5. There was a weak linear relation between leptin level with APACHE II & SOFA scores. There was non-significant difference in leptin level between survivors and non-survivors on day 0, 2 and 5. **Conclusion:** From our study we could suggest that leptin level in serum can be used as a good diagnostic marker in sepsis but not a good prognostic one.

1. Introduction:

One of the biggest global health issues and the main cause of intensive care unit (ICU) admissions is sepsis [1]. Sepsis-related mortality can reach up to 50% in developed countries. Sepsis is gaining attention from physicians and researchers due to its high death rates, complicated etiology, fast rising incidence, and also management challenges [2]. Biomarkers have a very vital importance in Sepsis diagnosis. However, no single biomarker will be able to fully capture the sepsis condition. [3].

The 16 kDa, 167-amino acid peptide leptin is primarily produced by adipocytes and has a role in controlling energy balance by informing the brain about the amount of adipose tissue in the body, which in turn controls food intake and energy expenditure [4]. Leptin is also a cytokine that is implicated in cytokine crosstalk and cell-mediated immunity [5].

Leptin levels increased in sepsis patients compared to controls, according to earlier research [6, 7]. Moreover, leptin level may be used for diagnosis and distinguishing sepsis from SIRS patients [8].

Aim of the study:

The aim of our study was to test the validity of serum leptin as a biomarker for diagnosis of sepsis and to correlate between the leptin level and sepsis prognosis and mortality.

2. Patients and Methods:

Our study was designed as a prospective case control study done during the period from **March 2023** to **February 2024** in critical care department, Beni-Suef university hospital and was enrolled on 25 critically ill patients diagnosed with sepsis. Ten healthy volunteers as a control group for serum leptin concentrations in a healthy population.

Inclusion criteria

Adult patients diagnosed as septic patients were enrolled in our study according to the Third International Consensus Definitions for Sepsis and Septic Shock [9].

Exclusion criteria

Patients ≤ 18 years were excluded from our study ,also patients received immune-suppressive drugs or corticosteroids before admission, patients received massive blood transfusion, patients with chronic renal failure or chronic liver failure and patients with expected ICU stay less than 24 hours.

Methods

All study patients were subjected to full clinical evaluation including history, physical examination, hemodynamic monitoring, routine laboratory investigations, cultures from sputum, blood, urine and from suspected sites of infection when needed and ABGs as needed. APACHE II and SOFA scores were evaluated for all patients. Imaging studies eg. Abdominal ultrasound, chest x-ray, CT…etc. were done as indicated.

Serum leptin was done on admission (day 0) as the initial sample, second day of admission (day 2) and fifth day of admission (day 5) for all included patients at 6 am while samples from the healthy controls were taken once.

Leptin measurement

Quantitative sandwich enzyme immunoassay was used to measure serum leptin in accordance with the manufacturer's instructions (immunospec corporation, USA).

Data analysis

We summarized data by using mean & standard deviation or frequency & percentage as appropriate. Parametric data were analyzed using either ANOVA or Student's t-tests while non-parametric data were analyzed using kruskal-wallis or Mann-Whitney tests. Bivariate pearson correlation to test association between variables**.** ROC curve analysis was done to predict the cut-off points of the test variables. A P-value of < 0.05 was considered significant.

Ethical considerations:

The study protocol was gained approval by the ethical committee of the faculty of medicine in Beni-Suef University.

3. Results:

Descriptive data

The age of the studied group ranged from 26 to 95 years with a mean of 62.2± 14.7 years. Sixteen (64%) patients were males and 9 (36%) patients were females. The BMI of the studied group ranged from 20.3 to 27.4 kg/m^2 with a mean of 25.8± 1.6 kg/m^2. Twenty eight percent of patients

(7) had multiple comorbidities, 24% (6) had diabetes mellitus, 16% (4) had hypertension, 12% (3) had ischemic heart disease, 4% (1) had COPD and 4% (1) had CVS.

As regards the source of infection; Eleven patients (44%) had chest infection, 4 (16%) had UTI, 2 (8%) had intra-abdominal infection, 1 (4%) had post-operative meningitis, 1 (4%) had diabetic foot and 6 (24%) had multiple source of infection. Table (1)

Table (1): Etiology of sepsis among studied group

Cause of sepsis	Number of patients	Percentage (%)
Chest infection	11	44%
Multiple source of infection	6	24%
UTI	4	16%
Intra-abdominal infection	2	8%
Post-operative meningitis	1	4%
Diabetic foot	1	4%

Blood, sputum and urine Cultures were withdrawn from all patients and other cultures according to the suspected source of infection and the results are shown in table (2).

Eighteen (72%) patients presented with sepsis while 7 (28%) presented with septic shock. Table (3)

APACHE II score ranged from 8 to 35 with a mean of 21±8 while SOFA score on admission (day 0) ranged from 2 to 13 with a mean of 6.1 ± 3.3, on day 2 it ranged from 1 to 12 with a mean of 5 ± 3.3 and on day 5 it ranged from 0 to 10 with a mean of 4.3 ± 3.5.Table (4)

Table (2): Cultures results among the study group Culture

Type of culture	Number of patients / positive results	Percent
Blood culture	25 12	48%
Sputum culture	25 19	76%
Urine culture	25 11	44%
Wound culture	4 3	75%

Table (3) Severity of sepsis among studied group

Item	Number of patients	Percentage (%)
Sepsis	18	72%
Septic shock	7	28%

Table (4) Scoring system among studied group

Item	Range	Mean ± SD
APACHE II	8-35	21±8
SOFA score		
Day 0	2-13	6.1±3.3
Day 2	1-12	5±3.3
Day 5	0-10	4.3±3.5

The hospital length of stay among the studied group ranged from 6 to 28 days with a mean of 13.8 ± 6.2 days. Of the studied group 14 (56%) patients needed mechanical ventilation, 12 (48%) needed vasopressors and 2 (8%) needed Hemodialysis.

Patients were segregated according to outcome into 13 (52%) survivors and 12 (48%) non-survivors. Table (5)

Table (5): Mortality among the studied group

Item	Number	Percentage (%)
Survivors	13	52%
Non-survivors	12	48%

In the studied group; on day 0 leptin levels ranged from 2.9 to 10.2 µg/L with a mean of 5.7 ± 1.9 µg/L, on day 2 leptin levels ranged from 19.2 to 60.4 µg/L with a mean of 40.2 ± 10.9 µg/L while leptin levels on day 5, it ranged from 7.1 to 20.2 µg/L with a mean of 13.2 ± 3.9 µg/L [table 6, figure 1]. In the control group; leptin level was measured once and ranged from 3.4 to 6.7 with a mean of 4.9 ± 1.2 µg/L. Table (7)

Table (6): Leptin level in the studied group

Leptin level	Range (µg/L)	Mean ± SD
Day 0	2.9-10.2	5.7±1.9
Day 2	19.2-60.4	40.2±10.9
Day 5	7.1-20.2	13.2±3.9

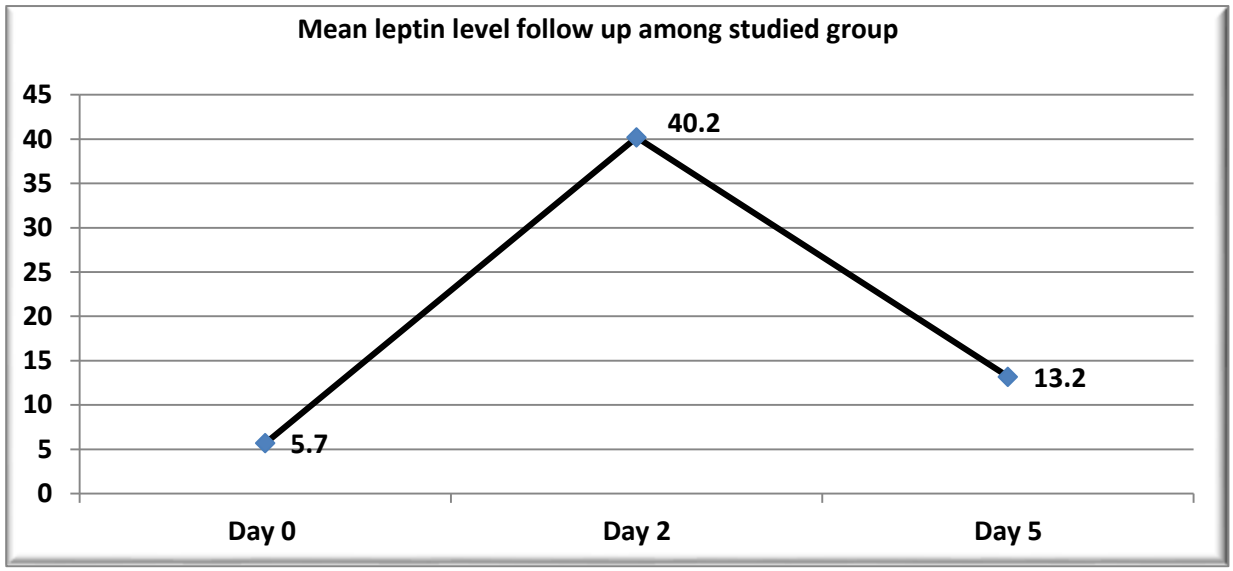


Figure (1): Mean leptin level follow up among studied group (µg/L).

Table (7): Leptin level among the control group (µg/L)

Item	Range	Mean ± SD
Leptin level	3.4-6.7	4.9 ± 1.2

Correlative data

On admission there was no significant correlation between serum leptin and either age, gender and comorbidities.

A significant positive correlation was detected between leptin levels on admission and BMI with r-value 0.71 & p-value <0.001. There was a non-significant correlation between leptin in the studied group (5.7±1.9 µg/L) and the control group (4.9 ± 1.2 µg/L) on admission (day 0) with a p-value of 0.2 while there was a highly significant correlation on day 2 and 5 (40.2 ± 10.9 µg/L Vs 4.9 ± 1.2 µg/L with a p-value < 0.001& 13.2 ± 3.9 µg/L Vs 4.9 ± 1.2 µg/L with a p-value < 0.001 respectively). Table (8)

Table (8) Leptin level in the studied group and control group

Leptin level (µg/L)	Study group (n=25)	Control group (n=10)	p-value	Significance
	Mean ± SD	Mean ± SD		
Day 0	5.7 ± 1.9	4.9 ± 1.2	0.20	NS
Day 2	40.2 ± 10.9		<0.001	HS
Day 5	13.2 ± 3.9		<0.001	HS

Leptin levels showed no statistically significant difference on day 0, day 2 and day 5 between sepsis and septic shock patients with p-values 0.30, 0.08 and 0.40 respectively. [Table 9, figure 2]

Table (9): Comparison of leptin levels between sepsis and septic shock patients

Leptin level (µg/L)	Sepsis	Septic shock	p-value	Significance
	Mean± SD	Mean± SD		
Day 0	5.5±1.8	6.4±2.2	0.30	NS
Day 2	37.8±11.3	46 ±7.2	0.08	NS
Day 5	12.9±0.4	14.6±3.8	0.40	NS

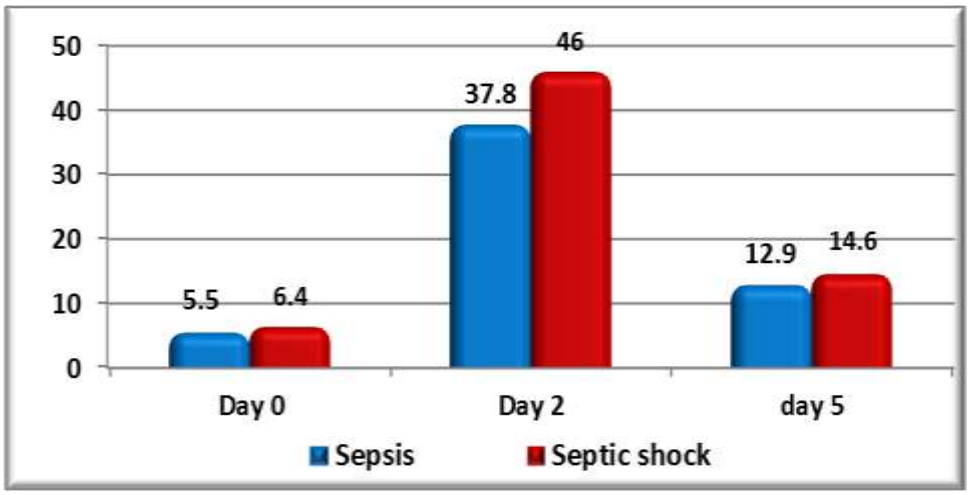


Figure (2): Comparison of leptin level among different degrees of sepsis in studied group

Our study showed a weak linear relation between leptin levels on admission & APACHE II score on admission with r-value 0.05 and p-value 0.8. There was a weak linear relation between mean leptin levels on day 0 with mean SOFA score on day o, mean leptin levels on day 2 with mean SOFA score on day 2 and mean leptin levels on day 5 with mean SOFA score on day 5 with r-values 0.11, 0.15 & 0.15 and p-values 0.6, 0.5 & 0.5 respectively. Our study showed a weak negative linear relation between leptin levels on day 0, day 2 and day 5 with the mean length of hospital stay with r-values -0.16, -0.19 & -0.29 and p-values 0.50, 0.40 and 0.20 respectively.

In survivors, the mean serum leptin levels were 5.8, 38.4 and 12.7µg/L in day 0, day 2 and day 5 respectively while in non survivors, serum leptin levels were 5.7, 42.2 and 13.8 on values 0.9, 0.4 and 0.5 on day 0, day 2 and day 5 respectively. (Table 10)

day 0, day 2 and day 5 respectively with p-

ROC curve was calculated for the use of serum leptin levels on day of admission, day 2 and day 5 as a marker for sepsis diagnosis. The optimal cut-off points of leptin to diagnose sepsis were 4.3µg/L with a sensitivity of 76 % and a specificity of 50 %, 22.5µg/L with a sensitivity of 96 % and a specificity of 90 % and 7.6µg/L with a sensitivity of 96 % and a specificity of 98 %, respectively. [Table 11, figure 3]

ROC curve was calculated for the use of serum leptin levels on day of admission, day 2 and day 5 as a prognostic marker for sepsis. The optimal cut-off points of leptin to predict mortality were 4.45µg/L with a sensitivity of 83% and a specificity of 39%, 35.7µg/L with a sensitivity of 75% and a specificity of 46 % and 11.3µg/L with a sensitivity of 83% and a specificity of 46%, respectively. [Table12, figure 3]

Table (10): Leptin level among survivors & non survivors

Leptin level (µg/L)	Survivors (n=13)	Non -survivors (n=12)	p-value	significance
	Mean ± SD	Mean ± SD		
Day 0	5.8±1.7	5.7±2.2	0.90	NS
Day 2	38.4±12.4	42.2±9.1	0.40	NS
Day 5	12.7±4.3	13.8±3.5	0.50	NS

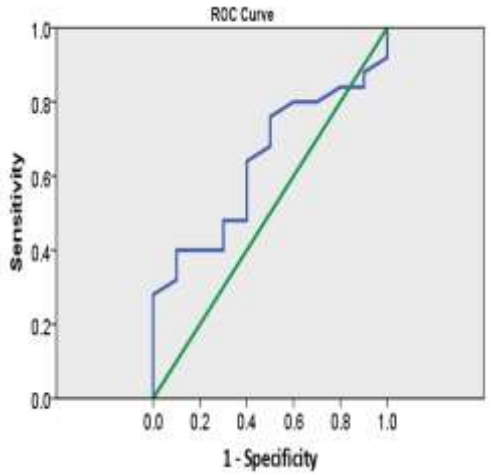
Table (11): ROC curve analysis for leptin as a diagnostic marker for sepsis

Leptin level	AUC	Cut-off point	Sensitivity	Specificity	p-value
Day 0	0.64	4.3	76%	50%	0.21
Day 2	0.93	22.5	96%	90%	<0.001
Day 5	0.97	7.6	96%	98%	<0.001

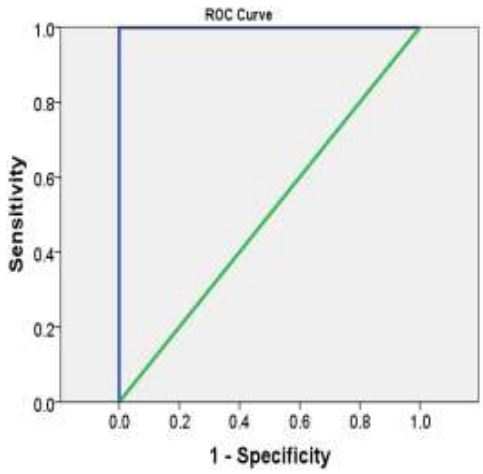
Table (12): ROC curve analysis for leptin as a prognostic marker for sepsis

Leptin level	AUC	Cut-off point	Sensitivity	Specificity	p-value
Day 0	0.44	4.45	83%	39%	0.61
Day 2	0.59	35.7	75%	46%	0.45
Day 5	0.62	11.3	83%	46%	0.31

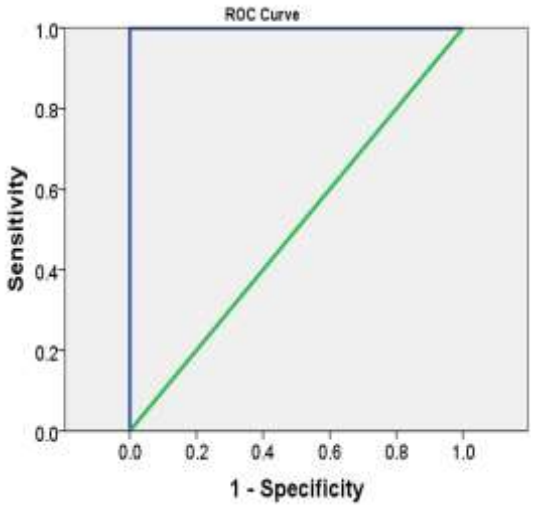
3a



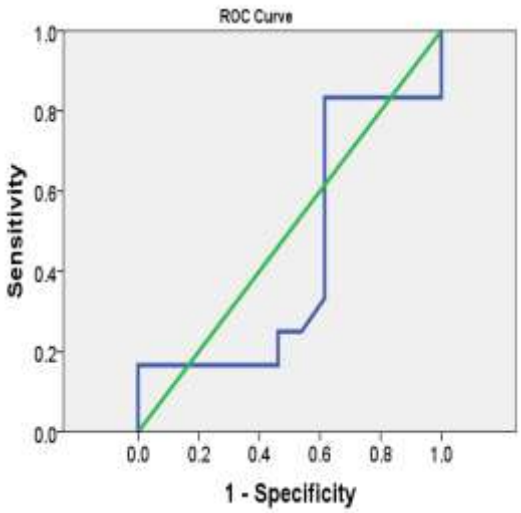
3b



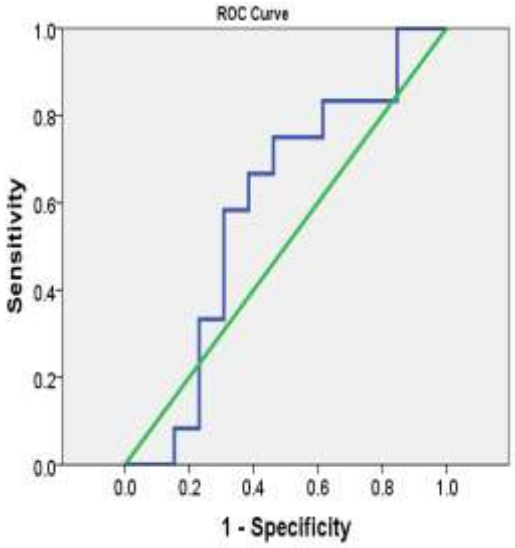
3c



3d



3e



3f

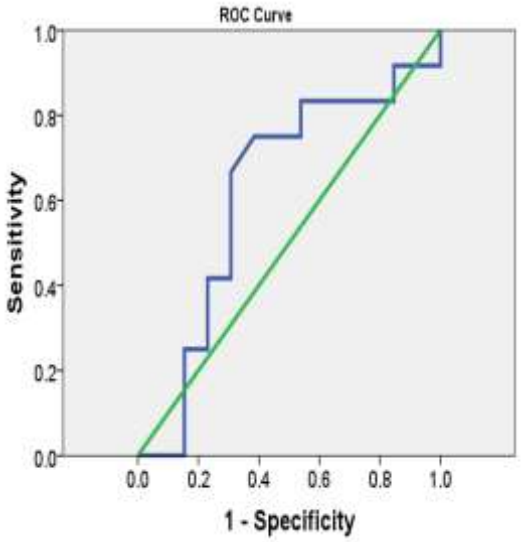


Figure (3a): ROC curve for leptin 0 as a marker for sepsis diagnosis . Figure (3b): ROC curve for leptin 2 as a diagnostic marker for sepsis. Figure (3c): ROC curve for leptin 5 as a diagnostic marker for sepsis. Figure (3d): ROC curve for leptin 0 as a prognostic marker for sepsis. Figure (3e): ROC curve for leptin 2 as a prognostic marker for sepsis. Figure (3f): ROC curve for leptin 5 as a prognostic marker for sepsis

4. Discussion:

Serum leptin concentrations in patients with sepsis were considerably higher than in controls in earlier studies [6, 10].

According to our study, there is no discernible correlation between age, gender, or any of the comorbidities and serum leptin levels. **Carlson et al.** 1999 [11] shown, in line with our study, that there was no significant correlation between serum leptin level and gender or age.. Also, Bornstein et al. 1998 [6] found no correlation between leptin with age in both sepsis and control groups.

Hillenbrand et al. 2010 [12] found no significant correlation between leptin level in patients serum with age but in contrast to our study, they reported increased leptin levels in females compared to those in males. The discrepancy in the above results may be due to different BMI of patients in each study and different number of patients (In our study we have only 9 female patients).

Leptin levels on admission and BMI showed a strong positive correlation in our study (r-value 0.71 & p-value <0.001). According to Hillenbrand et al. 2010 [12], there was a positive correlation (r = 0.64; p = < 0.001) between leptin levels and BMI, which is consistent with our findings.

we observed in our study that there was a non-significant difference in leptin between the studied group (5.7±1.9 µg/L) and the control group (4.9 ± 1.2 µg/L) on admission (day 0) with a p-value of 0.2 while we observed a high significant difference on day 2 and day 5 (40.2 ± 10.9 µg/L Vs 4.9 ± 1.2 µg/L with a p-value < 0.001 & 13.2 ± 3.9 µg/L Vs 4.9 ± 1.2 µg/L with a p-value < 0.001 respectively). Similar to our study, **Yousef et al.** 2010 [8] found that patients in the three groups had nearly the same admission blood leptin levels: 2.76 µg/L in the control group, 2.94 µg/L in the SIRS group, and 3.25 µg/L in the sepsis group. Leptin levels elevated significantly on the second day in both the sepsis and SIRS groups but not in the control group; the mean values in the control group were 3.4 µg/L, while in the SIRS group they were 30.5 µg/L and in the sepsis group 44.7 µg/L (P-value = 0.005). Same as our findings, **N. Faraga et al.** 2013 [13] found that a cut-off value of 38.05µg/L can be used to distinguish between sepsis and non-infectious SIRS based on the serum leptin level on the second day with a sensitivity of 93% and specificity of 100%.

Against our results, **Koch et al.** 2010 [14] measured the serum concentrations of soluble leptin-receptor and free leptin in 137 ICU patients upon admission. Their findings showed that there were no significant differences in serum leptin levels between patients with critical illness (n = 137, median 5.5 µg/L, range 0.4–49.6) and healthy controls (n = 26, median 6.6 µg/L, range 0.7–38.6), nor between ICU patients diagnosed with sepsis (n = 95, median 5.5 µg/L, range 0.4–49.6) and non-septic

etiology (n = 42, range 5.4 μg/L, range 0.4–45.1) of critical illness. Since they only measured leptin at the time of ICU admission, their results do not conflict with ours.

With p-values of 0.30, 0.08, and 0.40, respectively, our data demonstrated that there was no statistically significant difference in leptin levels between sepsis and septic shock on days 0, 2, and 5. On days 0, 2, and 5, the mean leptin level was 6.4±2.2 Vs 5.5±1.8, 46±7.2 Vs 37.8±11.3, and 14.6±3.8 Vs 12.9±0.4, respectively, greater in septic shock patients than in sepsis patients.

Parallel to our research, **Papathanassoglou et al.** (2001) examined 35 critically ill adult patients with SIRS who were either at risk for or had already developed MODS. They discovered that leptin levels did not correlate with severity and that patients with higher severity scores (MOF severity score≥8) could not be identified. Furthermore, the severity of sepsis did not significantly affect the level of leptin in the serum on independently, according to study by **Carlson et al.** 1999 [11]. On the other hand, 42 critically ill patients with bacteremia confirmed by culture were examined by **Arnalich et al.** Three groups of patients were selected: group 1 consisted of 28 patients suffering from severe sepsis, group 2 comprised of 14 patients experiencing septic shock, and group 3, the control group, consisted of 20 participants prior to elective surgery for a complicated peptic ulcer. Researchers discovered that patients diagnosed with sepsis or septic shock had significantly higher mean serial plasma leptin concentrations throughout the first 24 hours (14.3 varied from 7.4 to 27.5 μg/L) than controls (4.4 ranged from 2.4 to 6.9 μg/L, $P < 0.001$).also higher levels in septic shock patients (18.0 ranged from 11.4 to 27.5 μg/L) than in the sepsis group (10.2 ranged from 7.4 to 14.7 μg/L, $P < 0.01$). [7]

Our study showed a weak linear relation between leptin level on admission & APACHE II score on admission with p-value 0.8. In accordance with our study, **T. Quasim et al.** 2004 [16] found no significant correlation between leptin, adjusted for BMI, & APACHE II score (p-value 0.634). Also, Pehlivanli et al. 2011 [17] reported that leptin did not correlate well with APACHE II score. In contrast to our study, **Behnes et al.** 2012 [18] studied 104 patients suffering from severe sepsis and found a significant positive correlation between leptin and APACHE II score with r=0.28 & p-value 0.03. The difference in results may be due to increased number of studied patients.

Regarding SOFA score our study showed a weak linear relation between mean leptin levels on day 0 with mean SOFA score on day o, mean leptin levels on day 2 with mean SOFA score on day 2 and mean leptin levels on day 5 with mean SOFA score on day 5 with r-values 0.11, 0.15 & 0.15 and p-values 0.6, 0.5 & 0.5 respectively. **N. Farag et al.** 2013 [13] observed that, in keeping with our

investigation, there was a slight linear correlation between the SOFA score and leptin in the sepsis group (r= 0.39, P = 0.2; r= 0.36, P = 0.2; and r = 0.15, P = 0.6 for admission and days 2 and 4, respectively). According to **Hillenbrand et al.** 2016 [19], leptin did not significantly correlate (r= 0.02 & p=0.48) with the SAPS II score, which is consistent with our findings.

our study found no statistically significant correlation between the length of hospital stay and the mean leptin level on day 0, day 2, and day 5 (p-values 0.5, 0.4, and 0.2) respectively. The length of hospital stay ranged from 6 to 28 days, with a mean of 13.8±6.2 days. Hand by hand with our results, **Ahasic et al.** 2016 [20] found no correlation between leptin and length of hospital stay.

The mean serum leptin levels in survivors were 5.8, 38.4, and 12.7 µg/L on days 0, 2, and 5, respectively, while in non-survivors, the mean levels were 5.7, 42.2, and 13.8 µg/L on days 0, 2, and 5, with p-values of 0.9, 0.4, and 0.5 in day 0, day 2, and day 5, respectively. Our study did not find any significant correlation between survivors and non-survivors.

Similar to our study, **Tzanella et al.** 2006 [21] found that although leptin levels in survivors were 7.48 ±1.9 µg/L and nearly two times higher in non-survivors (14.35±7.44 Vs. 1.9 µg/L), the difference did not achieve statistical significance. During prolonged sepsis (>2 weeks from the onset of sepsis), patient leptin levels statistically decreased significantly from 10.2±2.5 to 6.25±1.7 µg/L, p=0.001. Leptin levels and their changes during sepsis were found to have no effect on the survival of septic patients, despite the fact that the decline was higher in non-survivors than in survivors (6.2±4.4 and 3.2±1.1 µg/L reduction from acute sepsis levels, respectively). However, there was no statistically significant difference between the two groups.

Furthermore, leptin levels did not significantly change between survivors and non-survivors, according to **Papathanassoglou et al.** 2001 [15]. According to **Salih et al.** 2011 [22], blood leptin levels in sepsis patients have little predictive significance.

Unlike our study, 230 adult patients with surgically diagnosed secondary peritonitis participated in a trial by **Riquelme et al.** 2008 [23], where two cohorts were created (leptin ≤ 10 µg/L and >10 µg/L). A 30-day period was allowed for either survival or death. It was determined whether leptin (≤ 10µg/L) and mortality were related. It was discovered that patients with moderate to severe secondary peritonitis have a poor prognostic sign in serum leptin levels < 10µg/L. The association between leptin levels and survival in 16 critically ill septic patients was also examined by **Bornstein et al.** 1998 [6]. They discovered that the mean leptin levels in survivors of acute sepsis (25.5±6.2 µg/L, n = 10 patients) were higher than in non-survivors (8.0±3.75 µg/L, n = 6

patients; p-value<0.01).

"Thus the value of leptin in predicting survival in critically ill patients is challenging and any effect of leptin on the outcome of septic patients may be confused by the concurrent alterations of other mediators, such as cytokines and hormones, and thus the application of multiple variable analysis is required" [15]. Variations in the number of patients, the source of the infection, the state of fasting and feeding, and the timing of sampling in each research may also account for differences in the results.

ROC curve was calculated for the use of serum leptin levels on day of admission, day 2 and day 5 as a sepsis diagnostic marker . The ideal cut-off points of leptin to diagnose sepsis were 4.3µg/L with a sensitivity of 76 % and a specificity of 50 %, 22.5µg/L with a sensitivity of 96 % and a specificity of 90 % and 7.6µg/L with a sensitivity of 96 % and a specificity of 98 %, respectively. Similar to our study, **Yousef et al.** 2010 [8] plotted a ROC curve for the use of leptin as a diagnostic marker for sepsis. The optimum cut-off point of leptin to diagnose sepsis was 5.1 µg/L with a sensitivity of 100 % and a specificity of 100%.

5. Conclusion:

Our study suggests that serum leptin level is not a strong prognosticator in sepsis, but it can be used as a good diagnostic marker.

Abbreviations

ICU: intensive care unit, SIRS: systemic inflammatory response syndrome, ABGs: arterial blood gases, APACHE II: acute Physiology and chronic health evaluation, SOFA: sequential organ failure assessment, CT: computed tomography, ROC: receiver operating characteristics, COPD: chronic obstructive pulmonary disease, CVS: cerebrovascular stroke, UTI: urinary tract infection, BMI: body mass index, MODS: multiple organ dysfunction syndrome, MOF: multiple organ failure, SAPS II: Simplified Acute Physiology Score.

6. References:

1. Nedeva, C., Menassa, J., & Puthalakath, H. (2019). Sepsis: inflammation is a necessary evil. Frontiers in cell and developmental biology, 7, 108.
2. Banta, J. E., Joshi, K. P., Beeson, L., et al. (2012). Patient and hospital characteristics associated with inpatient severe sepsis mortality in California, 2005–2010. *Critical care medicine*, *40*(11), 2960-2966.
3. Cohen, M., & Banerjee, D. (2023). Biomarkers in Sepsis: A Current Review of New Technologies. Journal of Intensive Care Medicine, 08850666231194535.
4. Pérez-Pérez, A., Sánchez-Jiménez, F., Vilariño-García, T., & Sánchez-Margalet, V. (2020). Role of leptin in inflammation and vice versa. International journal of molecular sciences, 21(16), 5887.

5. Mackey-Lawrence, N. M., & Petri, W. A. (2012). Leptin and mucosal immunity. Mucosal immunology, 5(5), 472-479.
6. La Cava, A. (2017). Leptin in inflammation and autoimmunity. Cytokine, 98, 51-58.
7. Iikuni, N., Kwan Lam, Q. L., Lu, L., Matarese, G., & Cava, A. L. (2008). Leptin and inflammation. Current immunology reviews, 4(2), 70-79.
8. Yousef, A. A. A. M., Amr, Y. M., & Suliman, G. A. (2010). The diagnostic value of serum leptin monitoring and its correlation with tumor necrosis factor-α in critically ill patients: a prospective observational study. Critical Care, 14(2), R33.
9. Singer, M., Deutschman, C. S., Seymour, C. W., et al. (2016). The third international consensus definitions for sepsis and septic shock (sepsis-3). Jama, 315(8), 801-810.
10. Chen, M., Wang, B., Xu, Y., et al. (2014). Diagnostic value of serum leptin and a promising novel diagnostic model for sepsis. Experimental and therapeutic medicine, 7(4), 881-886.
11. Carlson, G. L., Saeed, M., Little, R. A., et al. (1999). Serum leptin concentrations and their relation to metabolic abnormalities in human sepsis. American Journal of Physiology-Endocrinology And Metabolism, 276(4), E658-E662.
12. Hillenbrand, A., Knippschild, U., Weiss, M., Schrezenmeier, H., et al. (2010). Sepsis induced changes of adipokines and cytokines-septic patients compared to morbidly obese patients. BMC surgery, 10(1), 26.
13. Farag, N. A., Taema, K. M., Abdel-Latiff, E., et al. (2013). Differentiating sepsis from non-infective systemic inflammatory response syndrome: comparison between C-reactive protein and leptin. The Egyptian Journal of Critical Care Medicine, 1(3), 111-118.
14. Koch, A., Weiskirchen, R., Zimmermann, H. W., et al. (2010). Relevance of serum leptin and leptin-receptor concentrations in critically ill patients. Mediators of inflammation, 2010.
15. Papathanassoglou, E. D., Moynihan, J. A., Ackerman, M. H., et al. (2001). Serum leptin levels are higher but are not independently associated with severity or mortality in the multiple organ dysfunction/systemic inflammatory response syndrome: a matched case control and a longitudinal study. Clinical endocrinology, 54(2), 225-233.
16. Quasim, T., McMillan, D. C., Wallace, A. M., et al. (2004). The relationship between leptin concentrations, the systemic inflammatory response and illness severity in surgical patients admitted to ITU. Clinical Nutrition, 23(2), 233-238.
17. Pehlivanli, F., Ağalar, F., Ağalar, C., et al. (2011). The value of CRP, IL-6, leptin,

cortisol, and peritoneal caspase-3 monitoring in the operative strategy of secondary peritonitis. Ulus travma acil cerrahi Derg, 17(5), 390-395.

18. Behnes, M., Brueckmann, M., Lang, S., et al. (2012). Alterations of leptin in the course of inflammation and severe sepsis. BMC infectious diseases, 12(1), 217.
19. Hillenbrand, A., Xu, P., Zhou, S., et al. (2016). Circulating adipokine levels and prognostic value in septic patients. Journal of Inflammation, 13(1), 30.
20. Ahasic, A. M., & Pisani, M. (2016). Adipokines Early In Critical Illness. In A104. CRITICAL CARE: SEPSIS TRANSLATIONAL INSIGHTS (pp. A2730-A2730). American Thoracic Society.
21. Tzanela, M., Orfanos, S. E., Tsirantonaki, M., et al. (2006). Leptin alterations in the course of sepsis in humans. In Vivo, 20(4), 565-570.
22. Cesur, S., Şengül, A., Kurtoğlu, Y., et al. (2011). Prognostic value of cytokines (TNF-α, IL-10, Leptin) and C-reactive protein serum levels in adult patients with nosocomial sepsis. Journal of Microbiology and Infectious Diseases, 1(03).
23. Bracho-Riquelme, R. L., Reyes-Romero, M. A., Pescador, N., et al. (2008). A leptin serum concentration less than 10 ng/ml is a predictive marker of outcome in patients with moderate to severe secondary peritonitis. European Surgical Research, 41(2), 238-244.