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Validity of serum resistin level and Il-6 as prognostic biomarkers of decompensated liver cirrhosis in chronic hepatitis C virus patients

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Abstract

Background Decompensated liver cirrhosis (DLC) is now known as a chronic inflammatory process, evidenced by elevated levels of circulatory pro-inflammatory cytokines and chemokines which in turn lead to the development of more hepatic decompensation and multi-organ failure. Resistin has a pro-inflammatory effect through the production of several cytokines (e.g., IL-1, IL-6, IL-12, and TNF-α) and cell adhesion molecules. Interleukin-6 (IL-6) is a proinflammatory cytokine playing a crucial role in acute phase responses and in regulating immune reactions through activation and differentiation of T and B lymphocytes. The current study aimed to evaluate the value of serum resistin and IL-6 as biomarkers of DLC and their role as prognostic markers of complications in these patients.

Results This study was conducted on 90 patients divided into three groups: group I—30 patients with compensated cirrhosis (CLC); group II—40 patients with DLC; and group III consisted of 20 healthy controls. Serum resistin and IL-6 levels were statistically significantly higher in patients with DLC compared to patients with CLC at baseline. A cut-off value of > 302 pg/ml for serum resistin was found to discriminate between CLC and DLC with a specificity of 73.33% and sensitivity of 92.50% and a cut-off level of > 31 pg/mL for IL-6 differentiated between the two groups with a sensitivity of 85.0% and specificity of 76.67%. Patients with DLC were followed up for 3 months, 10 patients (25%) passed away, and 19 patients out of the remaining 30 (63.3%) patients developed complications including acute kidney injury, spontaneous bacterial peritonitis, variceal hemorrhage, encephalopathy, and hepatocellular carcinoma. Serum resistin and IL-6 were found to be significantly higher at baseline in those patients who developed complications or mortality after the follow-up period. In addition, there were positive correlations between IL-6 and resistin and MELD-NA and CRP.

Conclusion Serum resistin and IL-6 could be used as sensitive diagnostic and prognostic biomarkers of decompensated cirrhotic patients.

Keywords Decompensated liver cirrhosis, Prognosis, Resistin, Interleukin-6, Complications

Background

Liver cirrhosis (LC) is considered the final pathway of many chronic liver diseases. It is an irreversible process in its advanced stages [1]. It is one of the leading causes of death in adults [2]. LC is classified into compensated and decompensated based on its natural history. Compensated liver cirrhosis (CLC) is an asymptomatic

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phase, while decompensated liver cirrhosis (DLC) is characterized by the occurrence of clinical deterioration in the form of ascites, encephalopathy, and variceal hemorrhage [3].

Patients with DLC have a worse prognosis than CLC. The median survival was ≤ 6 months in decompensated cirrhosis patients with Child–Pugh score ≥ 12 or a Model for End-stage Liver Disease (MELD) score ≥ 21 [4].

It is now recognized that DLC is a chronic inflammatory process, evidenced by elevated levels of circulatory pro-inflammatory cytokines and chemokines [5]. This is thought to be caused by increased intestinal permeability and abnormal bacterial translocation. The release of pro-inflammatory molecules leads to the development of more hepatic decompensation and multi-organ failure [6].

Resistin is a protein formed of 108 amino acids that are named according to its supposed insulin resistance effect. It belongs to a family of cysteine-rich secretory proteins known as FIZZ (found in inflammatory zone proteins) [7]. Besides its metabolic role in increasing insulin resistance [8], resistin has a pro-inflammatory effect through the production of several cytokines (e.g., IL-1, IL-6, IL-12, and TNF-α) and cell adhesion molecules [9]. Although resistin is known to be secreted by human adipocytes, the most significant source appears to be mononuclear blood cells [10]. High resistin level is associated with chronic inflammatory diseases like rheumatoid arthritis, inflammatory bowel disease, and chronic kidney disease [11].

IL-6 is a proinflammatory cytokine playing a crucial role in acute phase responses and in regulating immune reactions through activation and differentiation of T and B lymphocytes [12]. IL-6 is considerably increased in pathological conditions like trauma, inflammation, and tumors [13].

Cirrhosis-associated immune dysfunction (CAID) occurring in patients with advanced cirrhosis is characterized by high levels of proinflammatory cytokines including IL-6 [14]. An association between the degree of decompensation of liver cirrhosis, IL-6, and serum resistin levels has been suggested [15, 16].

Methods

The aim of the work is to study the value of serum resistin and IL-6 as biomarkers of DLC and their role as prognostic markers to predict the development of complications in patients with DLC.

The current is a case–control study conducted on 70 patients with HCV-related liver cirrhosis divided into two groups. Group I consists of 30 patients with compensated cirrhosis. Group II contains 40 patients with decompensated liver cirrhosis. Twenty healthy subjects were taken as controls and comprised group III.

All patients were recruited from Tropical Medicine Department, Faculty of Medicine, Alexandria University, in the period between March 2021 and December 2021, after approval of the local ethical committee of Alexandria University. All patients were given an informed consent.

Sample size was calculated using med cal, according to Mariadi et al. [17] who found that IL-6 and resistin differentiated between patients with CLC and DLC with a minimum sample size of 70 patients.

All patients were subjected to detailed history taking and thorough clinical examination. Routine laboratory investigations were done including complete blood picture (CBC), C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), liver functions tests (LFTs) including international normalized ratio (INR), prothrombin activity (PA), serum bilirubin and albumin, renal functions tests (RFTs), and electrolytes including serum urea, creatinine, sodium, and potassium. Serum resistin level was measured by ELISA (enzyme-linked immunosorbent assay) technique [18] using Human RETN (Resistin) ELISA Kit and serum Il-6 was measured by ELISA technique [19] using Human Interleukin-6, IL-6 ELISA Kit.

Diagnosis of cirrhosis was based on FIB-4 score [20] as well as radiological evidence of cirrhosis by ultrasound evident by the shrunken liver with coarse echogenicity and manifestations of portal hypertension, ascites, and splenomegaly. FIB-4 > 3.25 was the cut-off value taken to diagnose liver cirrhosis. Patients with liver cirrhosis were classified according to Child–Pugh Score (C-P score) and MELD score to assess the degree of decompensation [21].

DLC patients were subjected to follow-up after 3 months to assess mortality and development of complications namely acute kidney injury after exclusion of causes unrelated to liver cirrhosis defined by either an absolute increase in serum creatinine (SCr) of more than or equal to 0.3 mg/dl in less than 48 h or a percentage increase in SCr of more or equal to 50% (1.5-fold from baseline) in less than 7 days [22], variceal hemorrhage, spontaneous bacterial peritonitis diagnosed based on neutrophil count in ascitic fluid of > 250/mm^3 [23], and hepatocellular carcinoma, whom diagnosis was based on imaging techniques obtained by multiphasic CT or dynamic contrast-enhanced MRI

showing arterial phase hyperenhancement (APHE) with washout in the portal venous or delayed phases [24].

Exclusion criteria

Patients with diabetes mellitus (DM), chronic kidney disease (CKD), malignancy, coronary artery disease, rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and those taking immunosuppressive drugs or steroids were excluded.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0.(Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Shapiro–Wilk test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

Table 1 Baseline characteristics of patients and controls

	Group I ($n=30$)	Group II ($n=40$)	Group III ($n=20$)	Test of sig	p
Sex					
Male	20 (66.7%)	23 (57.5%)	10 (50%)	$\chi^2=1.434$	0.488
Female	10 (33.3%)	17 (42.5%)	10 (50%)		
Age (years)	58.50 ± 8.44	59.15 ± 9.18	54.05 ± 8.11	$F=2.430$	0.094
RBCs (10^6/ul)	4.16 ± 0.50	3.31 ± 0.66	4.72 ± 0.54	$F=42.80^*$	$<0.001^*$
Sig. bet. grps	$p_1<0.001^*$, $p_2=0.004^*$, $p_3<0.001^*$				
WBCs (10^3/ul)	4.77 ± 1.91	4.38 ± 1.53	5.93 ± 1.29	$F=6.123^*$	0.003^*
Sig. bet. grps	$p_1=0.586$, $p_2=0.040^*$, $p_3=0.002^*$				
Platelets (10^3/ul)	118.5 ± 30.91	97.40 ± 34.40	293.15 ± 54.90	$F=182.44^*$	$<0.001^*$
Sig. bet. grps	$p_1=0.069$, $p_2<0.001^*$, $p_3<0.001^*$				
AST (U/L)	29 (14–50)	45 (22–186)	20.5 (14–32)	$H=54.26^*$	$<0.001^*$
Sig. bet. grps	$p_1<0.001^*$, $p_2=0.011^*$, $p_3<0.001^*$				
ALT (U/L)	25 (11–38)	31 (14–115)	23.5 (19–30)	$H=21.39^*$	$<0.001^*$
Sig. bet. grps	$p_1<0.001^*$, $p_2=0.496$, $p_3<0.001^*$				
S. Albumin (g/dl)	3.85 (3.5–4.9)	2.6 (2.1–3.4)	4.2 (3.6–5.0)	$H=68.546^*$	$<0.001^*$
Sig. bet. grps	$p_1<0.001^*$, $p_2=0.131$, $p_3<0.001^*$				
T. bilirubin (mg/dl)	0.8 (0.2–1.3)	2.4 (0.7–14.1)	0.9 (0.50–1.10)	$H=57.66^*$	$<0.001^*$
Sig. bet. grps	$p_1<0.001^*$, $p_2=0.600$, $p_3<0.001^*$				
INR	1.10 (0.95–1.29)	1.56 (1.12–2.60)	1.0 (0.90–1.18)	$H=68.02^*$	$<0.001^*$
Sig. bet. grps	$p_1<0.001^*$, $p_2=0.066$, $p_3<0.001^*$				
Serum urea (mg/dl)	29 (10–53)	42.5 (9–139)	31.5 (24–44)	$H=10.561^*$	0.005^*
Sig. bet. grps	$p_1=0.002^*$, $p_2=0.460$, $p_3=0.047^*$				
S. creatinine (mg/dl)	0.85 (0.5–1.4)	1.3 (0.6–3.8)	0.9 (0.7–1.3)	$H=19.090^*$	$<0.001^*$
Sig. bet. grps	$p_1<0.001^*$, $p_2=0.524$, $p_3=0.003^*$				
CRP	6.60 (1.30–15.0)	38.90 (6.0–80.0)	4.45 (2.60–6.10)	$H=65.104^*$	$<0.001^*$
Sig. bet. grps	$p_1<0.001$*, $p_2=0.006$*, $p_3<0.001$*				
MELD-NA	10.0 (7.0–14.0)	22.0 (10.0–33.0)	8.0 (6.0–11.0)	$H=66.551^*$	$<0.001^*$
Sig. bet. grps	$p_1<0.001$*, $p_2=0.042$*, $p_3<0.001$*				
FIB-4	**2.82 (2.59–3.26)**	**5.72 (2.19–20.40)**	**0.74 (0.48–1.22)**	$H=60.737^*$	$<0.001^*$
Sig. bet. Grps	$p_1<0.001$*, $p_2<0.001$*, $p_3<0.001$*				
Resistin level (pg/ml)	259.5 (110–410)	638 (236–923)	62 (45–81)	$H=70.53^*$	$<0.001^*$
Sig. bet. grps	$p_1<0.001^*$, $p_2=0.001^*$, $p_3<0.001^*$				
IL-6 level (pg/ml)	27 (11–45)	53.5 (17–131)	7.2 (4.9–10.2)	$H=65.96^*$	$<0.001^*$
Sig. bet. grps	$p_1<0.001^*$, $p_2=0.001^*$, $p_3<0.001^*$				

p_1, p value for comparing group I and group II

p_2, p value for comparing group I and group III

p_3, p value for comparing group II and group III

RBCs Red blood cells; *WBCs* White blood cells; *AST* Aspartate transaminase; *ALT* Alanine transaminase; *INR* International normalized ratio; *MELD-NA* Model of end-stage liver disease; *CRP* C-reactive protein; *F* One way ANOVA test; *H* Kruskal Wallis test

* Statistically significant at $p \leq 0.05$

The used tests were:

1. Chi-square test
   For categorical variables, to compare different groups.
2. Fisher's exact or Monte Carlo correction
   Correction for chi-square when more than 20% of the cells have an expected count of less than 5.
3. F-test (ANOVA)
   For normally distributed quantitative variables, to compare between more than two groups, and post hoc test (Tukey) for pairwise comparisons.
4. Mann–Whitney test
   For abnormally distributed quantitative variables, to compare between two studied groups.
5. Kruskal–Wallis test
   For abnormally distributed quantitative variables, to compare between more than two studied groups, and post hoc (Dunn's multiple comparisons test) for pairwise comparisons.
6. Spearman coefficient
   To correlate between two distributed abnormally quantitative variables.
7. Receiver operating characteristic curve (ROC)
   It is generated by plotting sensitivity (TP) on *Y* axis versus 1-specificity (FP) on *X* axis at different cut-off values. The area under the ROC curve denotes the diagnostic performance of the test. Area of more than 50% gives acceptable performance and area of about 100% is the best performance for the test. The ROC curve allows also a comparison of performance between two tests.
8. Logistic regression
   To detect the most affecting factor for affecting complication.

Results

This study was conducted on 90 candidates in the Alexandria Main University Hospital, Tropical Medicine Department, categorized into 3 groups: group I—30 patients with compensated liver cirrhosis; group II—40 patients with decompensated liver cirrhosis; and group III—20 healthy controls. All the patients in group I were Child–Pugh Class A. While regarding group II, 14 patients were Child–Pugh score B and the other 26 patients were Child–Pugh class C. Serum resistin and IL-6 were statistically significantly higher in group II than groups I and III. Table 1 summarizes the baseline characteristics of patients and controls. All patients included in the study had HCV-related chronic liver disease and all of them were treated for HCV at different time frames before the study. All patients were anti-HCV positive, and PCR for HCV negative.

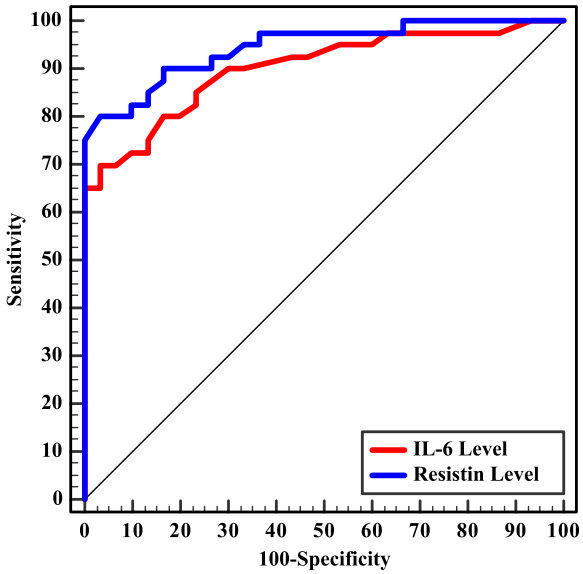

Fig. 1 ROC curve for resistin level and IL-6 level to discriminate between decompensated liver cirrhosis patients ($n=40$) from compensated liver cirrhosis ($n=30$) (group II vs I)

Table 3 Correlation between resistin level, IL-6 level, and different parameters in group II (decompensated liver cirrhosis) ($n=40$)

	Resistin level		IL-6 level	
	r_s	*P*	r_s	*p*
Child–Pugh class	0.740	< 0.001*	0.644	< 0.001*
MELD-NA	0.777	< 0.001*	0.637	< 0.001*
CRP	0.733	< 0.001*	0.852	< 0.001*
FIB-4	0.476	0.002*	0.575	< 0.001*
Resistin vs. IL-6	0.837	< 0.001*		

* Statistically significant at $p \leq 0.05$

Table 4 Distribution of decompensated cirrhosis cases according to mortality and complication development after 3 months

	No	%
Mortality	10	25.0
Complication ($n=30$, after excluding fatalities)		
No	11	36.7
Yes	**19**	**63.3**
Complications		
AKI	5	16.7
SBP	8	26.7
Variceal hemorrhage	3	10.0
Encephalopathy	6	20.0
HCC	5	16.7

AKI Acute kidney injury; *SBP* Spontaneous bacterial peritonitis; *HCC* Hepatocellular carcinoma

Table 2 Validity (AUC, sensitivity, specificity) for resistin level, IL-6 level, and combined resistin and IL-6 to discriminate between DLC patients ($n=40$) from CLC patients ($n=30$) (group II vs I)

	AUC	p	95% C.I	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
IL-6 level	0.901	< 0.001*	0.830–0.972	> 31	85.0	76.67	82.9	79.3	81.43
Resistin Level	0.945	< 0.001*	0.896–0.994	> 302	92.50	73.33	82.2	88.0	84.28
Combined IL-6 and resistin	0.945	< 0.001*	0.896–0.994	-	92.50	73.33	82.2	88.0	84.28

* Statistically significant at $p \leq 0.05$

At a cut-off value of > 302 pg/ml serum resistin was found to discriminate between compensated and decompensated cirrhosis with specificity of 73.33% and sensitivity of 92.50% as shown in Fig. 1 and Table 2. Regarding IL-6, a cut-off level of > 31 pg/mL differentiated between the two groups with a sensitivity of 85.0% and specificity of 76.67% as shown in Fig. 1 and Table 2.

Serum resistin and IL-6 showed a significant positive correlation with each other as shown in Table 3, in addition to positive correlations with CRP, MELD-NA, FIB-4, and Child–Pugh score as shown in Table 3.

After follow-up of 40 patients with DLC after 3 months, 10 patients (25%) passed away and out of the remaining 30 patients, 19 (63.3%) patients developed complications including acute kidney injury, spontaneous bacterial peritonitis, variceal hemorrhage, and encephalopathy while 11 patients did not develop any complication as shown in Table 4. As regards the 10 patients who passed away, they died due to complications related to cirrhosis namely acute on chronic liver failure, sepsis, and variceal hemorrhage (Table 5).

A cut-off value of > 480 pg/ml for serum resistin was found to predict the development of complications in DLC at 3-month follow-up period with 90.91% and 96.55% sensitivity and specificity respectively. Regarding IL-6, a cut-off level of > 37 pg/mL was found with a sensitivity of 93.10% and specificity of 90.91% as shown in Table 6.

Table 5 Relation between serum resistin and IL-6 level with mortality and complication in group II (decompensated liver cirrhosis) ($n=40$)

	N	Resistin level Median (Min.–Max.)	IL-6 level Median (Min.–Max.)
Mortality			
No	**30**	564 (236–917)	48 (17–86)
Yes	**10**	833 (649–923)	90 (77–131)
U (p)		31.0* (< 0.001*)	5.500* (< 0.001*)
Complication			
No	**11**	346 (236–510)	31 (17–39)
Yes	**19**	691 (410–917)	55 (36–86)
U (p)		5.500* (< 0.001*)	2.50* (< 0.001*)

U, Mann–Whitney test

* Statistically significant at $p \leq 0.05$

Discussion

It is well known now that decompensated liver cirrhosis is a chronic inflammatory status [5]. Resistin and IL-6 levels which are both known to have pro-inflammatory effects were studied to assess their association with decompensated liver cirrhosis and evaluate their potential value to predict the development of complications in those patients (Table 7).

In our study, there was a statistically significant higher level of serum resistin in patients with decompensated liver cirrhosis compared to compensated patients. At baseline, higher levels of resistin were observed in patients with decompensated liver cirrhosis who developed complications or died after a period of 3 months' follow-up. In addition, significant positive correlations were found between resistin level and IL-6 and both were correlating positively to MELD score, C-P score, and CRP. This was in concordance with Yagmur et al. who found that serum resistin was correlated positively with markers of inflammation such as tumor necrosis factor-alpha (TNF-α) or C-reactive protein (CRP), as well as with clinical complications, e.g., portal hypertension [25]. Also, Mariadi et al. found the same positive correlation between resistin level and IL-6 and CRP levels [17].

Human resistin is among the inflammatory regulators for guiding the subsequent actions of inflammation in macrophages, peripheral blood mononuclear cells (PBMNs), and vascular cells. When these cells are stimulated with recombinant human resistin, they produce tumor necrosis factor-alpha (TNF-α), IL-6, IL-12, and monocyte chemotactic protein-1 (MCP-1) through nuclear factor kappa B (NFκB)-mediated pathway [26]. Human resistin expression is elevated during the pathological conditions of inflammation. Circulatory resistin level has been positively correlated with common inflammatory and fibrinolytic biomarkers such as CRP, TNF-a, and IL-6 [27].

Table 6 Validity (AUC, sensitivity, specificity) for IL-6 level and resistin level to discriminate DLC who developed complications ($n=29$) from non-complicated DLC ($n=11$) patients at follow-up

	AUC	p	95% C.I	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
IL-6 level	0.992	< 0.001*	0.973–1.011	> 37	96.55	90.91	96.6	90.9	95.0
Resistin level	0.983	< 0.001*	0.952–1.013	> 480	93.10	90.91	96.4	83.3	92.5

* Statistically significant at $p \leq 0.05$

Moreover, these findings were in concordance with what Costa et al. who studied biomarkers of systemic inflammation across different stages of advanced chronic liver disease (ACLD) and found statistically significant higher levels of IL-6 in decompensated stages compared to compensated stages [28].

It was also noted that IL-6 levels showed a statistically significant positive correlation with CRP levels. This was in concordance with Turco et al. who demonstrated that CRP levels increased progressively across stages of compensated and decompensated liver cirrhosis patients [29].

Table 7 Univariate and multivariate logistic regression analysis for complicated and mortality regarding different factors ($n=29$ vs. 11)

	Non complication® ($n=11$)	Complicated and mortality ($n=29$)	Univariate		Multivariate	
			OR (LL–UL 95%C.I)	*p*	OR (LL–UL 95%C.I)	*p*
Sex						
Male	5 (45.5%)	18 (62.1%)	1.964 (0.482–7.995)	0.346		
Female	6 (54.5%)	11 (37.9%)	0.509 (0.125–2.073)	0.346		
Age (years)	56.45 ± 11.55	60.17 ± 8.12	1.046 (0.968–1.130)	0.255		
Hemoglobin	9.97 ± 2.04	9.39 ± 1.12	0.734 (0.434–1.242)	0.250		
WBCs	4.59 ± 2.07	4.30 ± 1.31	0.885 (0.564–1.386)	0.592		
Platelets	109.7 ± 41.35	92.72 ± 30.90	0.985 (0.963–1.006)	0.166		
CRP	17.96 ± 11.81	41.38 ± 14.96	1.119 (1.045–1.199)	0.001*	2.011 (–)	0.999
ESR	36.73 ± 8.72	41.93 ± 7.89	1.103 (0.988–1.231)	0.080		
AST	43.82 ± 11.83	62.48 ± 41.96	1.027 (0.985–1.072)	0.211		
ALT	29.0 ± 10.17	40.17 ± 23.43	1.054 (0.980–1.134)	0.153		
ALP	135.9 ± 38.30	187.9 ± 50.95	1.025 (1.006–1.045)	0.010*	1.070 (–)	1.000
S. Albumin (gm/l)	29.91 ± 2.59	25.10 ± 1.59	0.136 (0.025–0.743)	0.021*	0.0 (–)	0.999
Total bilirubin	1.47 ± 0.52	3.72 ± 2.73	9.776 (1.942–49.196)	0.006*	794.932(–)	1.000
P.T	15.65 ± 1.74	18.71 ± 3.20	1.786 (1.152–2.768)	0.009*	273,642 (–)	0.999
INR	1.38 ± 0.16	1.68 ± 0.29	398.2 (4.967–3193)	0.007*	0.0 (–)	0.999
Serum urea	36.08 ± 12.83	47.47 ± 25.16	1.032 (0.988–1.077)	0.158		
Serum creatinine	1.05 ± 0.38	1.35 ± 0.57	6.834 (0.714–65.435)	0.095		
Sodium	135.0 ± 3.66	131.0 ± 4.35	0.788 (0.646–0.962)	0.019*	0.005 (–)	1.000
Potassium	3.77 ± 0.50	4.24 ± 1.18	3.476 (0.642–18.826)	0.148		
Child–Pugh class	8.09 ± 0.83	11.03 ± 1.59	4.495 (1.739–11.619)	0.002*	0.143 (–)	1.000
APRI score	1.14 ± 0.52	1.83 ± 1.26	2.942 (0.772–11.209)	0.114		
FIB-4	5.20 ± 3.49	6.92 ± 4.03	1.170 (0.906–1.510)	0.229		
MELD-NA	15.73 ± 3.85	23.52 ± 4.07	1.655 (1.198–2.285)	0.002*	0.006 (–)	0.999
Resistin level	355.1 ± 83.67	719.7 ± 143.3	1.024 (1.006–1.043)	0.009*	1.072 (–)	0.999
IL-6 level	30.73 ± 6.34	69.17 ± 21.87	1.80 (0.957–3.383)	0.068	0.996 (–)	1.000

Quantitative data was expressed using mean ± SD

Qualitative data was expressed using number (%)

OR Odds ratio; *C.I* Confidence interval; *LL* Lower limit; *UL* Upper limit

p, *p* value for odds ratio for comparing the studied groups

* Statistically significant at $p \leq 0.05$

In our research, decompensated cirrhosis patients who have IL-6 levels more than 37 pg/ml at baseline showed a statistically significant higher probability to develop complications and mortality in 3-month period of follow-up. This was in concordance with Costa et al. who found that decompensated patients.with high IL-6 of more than 14 pg/ml showed a significantly higher probability of liver-related death/LT [28]. The difference in the cut-off valve of IL-6 to predict the probability of complications may be related to the difference in the serological kits for IL-6 used. The smaller sample size in our study may be another contributing factor to this difference.

In addition, higher levels of resistin levels were found in decompensated cirrhosis patients who developed complications and mortality in 3 months of follow-up with cut-off predictive value of more than 480 pg/ml. This was in line with Yagmur et al. who showed that high resistin levels were an unfavorable prognostic indicator for overall survival with serum resistin value of more than 5 µg/L [25]. The difference in the cut-off value is likely related to different serological kits used to measure serum resistin and it may be related to the differences in the studied population on which the research was conducted.

However, unlike our observation, Da Silva et al. found that resistin levels were not associated with survival in cirrhotic patients [30]. This may be attributed to due to the smaller proportion of patients with more severe liver diseases, only 3 out of 122 patients were Child–Pugh C in this study. It may be also due to differences in the etiology of cirrhosis across different studies.

Limitation of study

- Small sample size
- Longer period of follow-up required to determine a more precise cut-off value for the prediction of complications.

Conclusion

Serum IL-6 and resistin could be used as sensitive diagnostic and prognostic biomarkers of decompensation in cirrhotic patients. Furthermore, the significant correlation of serum resistin and IL-6 with Child–Pugh and MELD score could suggest that they can be used as a tool to follow up the clinical outcomes of patients with liver cirrhosis and prioritize listing for liver transplantation.

Abbreviations

LC	Liver cirrhosis
CLC	Compensated liver cirrhosis
DLC	Decompensated liver cirrhosis
MELD	Model for end-stage liver disease
FIZZ	Found in inflammatory zone proteins
IL-6	Interleukin-6
CAID	Cirrhosis associated immune dysfunction
RETN	Resistin
ELISA	Enzyme-linked immunosorbent assay
CRP	C-reactive protein
C-P	Child-Pugh Score
APHE	Arterial phase hyperenhancement
PBMNs	Peripheral blood mononuclear cells
TNF-α	Tumor necrosis factor-alpha
MCP-1	Monocyte chemotactic protein-1
NFκB	Nuclear factor kappa B
ACLD	Advanced chronic liver disease

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Authors' contributions

1- Ayman F. El-Shayeb (MD): Conceptualization, follow-up of data collection, manuscript revision and editing. 2- Akram A. Degheidy (MD): Laboratory work, results analysis, manuscript revision and editing. 3. Sawsan El-Mallah (MD): Manuscript revision and editing. 4. John Farid *(corresponding author): Patients' data collection, results generation and analysis, and major writing of the manuscript. 5. Amany N. Abbasy (MD): Follow-up of patients' data collection, results analysis, and editing and reviewing of the manuscript.

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Availability of data and materials

All data used, generated, or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study has been approved by the Faculty of Medicine, Alexandria University Ethics Committee. The present work had been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The serial registration number for this study is 0201452. All patients had given an informed written consent stating the title, procedure, and purpose of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Tsochatzis EA, Bosch J, Burroughs AK (2014) Liver cirrhosis. Lancet 383(9930):1749–1761

2. Scaglione S, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A et al (2015) The epidemiology of cirrhosis in the United States. J Clin Gastroenterol 49(8):690–696
3. Gioia S, Nardelli S, Pasquale C, Pentassuglio I, Nicoletti V, Aprile F et al (2018) Natural history of patients with non cirrhotic portal hypertension: Comparison with patients with compensated cirrhosis. Dig Liver Dis 50(8):839–844
4. Salpeter SR, Luo EJ, Malter DS, Stuart B. Systematic review of noncancer presentations with a median survival of 6 months or less. The American journal of medicine. 2012;125(5):512. e1-. e16
5. Clària J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M et al (2016) Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. Hepatology 64(4):1249–1264
6. Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V (2015) Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol 63(5):1272–1284
7. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM et al (2001) The hormone resistin links obesity to diabetes. Nature 409(6818):307–312
8. Steppan C, Lazar MA (2004) The current biology of resistin. J Intern Med 255:439–447
9. Silswal N, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S, Ehtesham NZ (2005) Human resistin stimulates the pro-inflammatory cytokines TNF-α and IL-12 in macrophages by NF-κB-dependent pathway. Biochem Biophys Res Commun 334(4):1092–1101
10. Coelho M, Oliveira T, Fernandes R (2013) Biochemistry of adipose tissue: an endocrine organ. Arch Med Sci 9(2):191
11. Nagy K, Nagaraju SP, Rhee CM, Mathe Z, Molnar MZ (2016) Adipocytokines in renal transplant recipients. Clin Kidney J 9(3):359–373
12. Jacob N, Stohl W (2011) Cytokine disturbances in systemic lupus erythematosus. Arthritis Res Ther 13(4):1–11
13. Del Campo JA, Gallego P, Grande L (2018) Role of inflammatory response in liver diseases: therapeutic strategies. World J Hepatol 10(1):1
14. Albillos A, Lario M, Álvarez-Mon M (2014) Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol 61(6):1385–1396
15. Wiese S, Mortensen C, Gøtze JP, Christensen E, Andersen O, Bendtsen F et al (2014) Cardiac and proinflammatory markers predict prognosis in cirrhosis. Liver Int 34(6):e19–e30
16. Fischer P, Grigoras C, Bugariu A, Nicoara-Farcau O, Stefanescu H, Benea A et al (2019) Are presepsin and resistin better markers for bacterial infection in patients with decompensated liver cirrhosis? Dig Liver Dis 51(12):1685–1691
17. Mariadi IK, Koncoro H, Wibawa IDN (2020) C-Reactive Protein and Interleukin-6 Correlated with Resistin Level in Liver Cirrhosis. Indones J Gastroenterol Hepatol Dig Endosc 21(1):17–21
18. Degawa-Yamauchi M, Bovenkerk JE, Juliar BE, Watson W, Kerr K, Jones R et al (2003) Serum resistin (FIZZ3) protein is increased in obese humans. J Clin Endocrinol Metab 88(11):5452–5455
19. Helle M, Boeije L, de Groot E, de Vos A, Aarden L (1991) Sensitive ELISA for interleukin-6: detection of IL-6 in biological fluids: synovial fluids and sera. J Immunol Methods 138(1):47–56
20. Procopet B, Berzigotti A (2017) Diagnosis of cirrhosis and portal hypertension: imaging, non-invasive markers of fibrosis and liver biopsy. Gastroenterol Rep 5(2):79–89
21. Christensen E (2004) Prognostic models including the Child-Pugh, MELD and Mayo risk scores—where are we and where should we go? J Hepatol 41(2):344–350
22. Khwaja A (2012) KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 120(4):c179–c184
23. Rimola A, García-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B et al (2000) Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. J Hepatol 32(1):142–153
24. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK et al (2001) Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. J Hepatol 35(3):421–30
25. Yagmur E, Trautwein C, Gressner A, Tacke F (2006) Resistin serum levels are associated with insulin resistance, disease severity, clinical complications, and prognosis in patients with chronic liver diseases. Am J Gastroenterol 101(6):1244–1252
26. Filková M, Haluzík M, Gay S, Šenolt L (2009) The role of resistin as a regulator of inflammation: Implications for various human pathologies. Clin Immunol 133(2):157–170
27. Qi Q, Wang J, Li H, Yu Z, Ye X, Hu FB et al (2008) Associations of resistin with inflammatory and fibrinolytic markers, insulin resistance, and metabolic syndrome in middle-aged and older Chinese. Eur J Endocrinol 159(5):585–593
28. Costa D, Simbrunner B, Jachs M, Hartl L, Bauer D, Paternostro R et al (2021) Systemic inflammation increases across distinct stages of advanced chronic liver disease and correlates with decompensation and mortality. J Hepatol 74(4):819–828
29. Turco L, Garcia-Tsao G, Magnani I, Bianchini M, Costetti M, Caporali C et al (2018) Cardiopulmonary hemodynamics and C-reactive protein as prognostic indicators in compensated and decompensated cirrhosis. J Hepatol 68(5):949–958
30. da Silva TE, Costa-Silva M, Correa CG, Denardin G, Alencar MLA, Coelho MSPH et al (2018) Clinical significance of serum adiponectin and resistin levels in liver cirrhosis. Ann Hepatol 17(2):286–299

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