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Association Abnormal Levels of Serum Interleukin-33, Interleukin-23 with Oxidant-Antioxidants Status in patients with Acute Liver Failure

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Abstract: Acute liver failure (ALF) is not itself a disease, but a condition that develops rapidly in response to some forms of liver injury. There is no evidence to prove an association between serum IL-33 with oxidant- antioxidant status in patients of liver failure. The present study aimed to evaluate the possible association between these parameters and to investigation the prognostic role of interleukin-33 in liver failure disease by using the ROC curve. This study includes (30 patients and 30 controls ((were 17 men and 13 female)). During the period of 2021- 2022, patients and controls aged 30-55 years. The results showed that there is a significant increase in the serum levels of (MDA, NO, CP , IL-33 and IL-23) in patients group in comparison with controls group Furthermore, it was found that there is a positive correlation between IL-33 and (IL-23, MDA, NO and Cp).The ROC curve demonstrated that the levels of (IL-33, IL-23, MDA, NO and CP) have exhibited an good method for discriminating' between healthy individuals and patients with acute liver failure .In Conclusion, our findings indicated that there is an association between abnormal serum IL-33 levels and Oxidant-Antioxidants Status. Moreover, the level of IL-33 can consider an early prediction biomarker for gestational diabetes. The use of ROC curve analysis confirmed thatIL-33 is effective for the diagnosis of liver failure.

Keywords: Acute Liver Failure, IL-33, IL-23, Oxidant-Antioxidants Status.

I. I. INTRODUCTION

Acute liver failure (ALF) is not itself a disease, but a condition that develops rapidly in response to some forms of liver injury. Clinically, ALF is defined as reduced blood clotting and altered mental function, the latter beginning within just days or weeks of initial symptoms (e.g., jaundice, coagulopathy, etc.), in the absence of previously established liver disease(Lee ,2008; Lee ,2012). Acute liver failure is a rare and severe consequence of abrupt hepatocyte injury, and can evolve over days or weeks to a lethal outcome. A variety of insults to liver cells result in a consistent pattern of rapid-onset elevation of aminotransferases, altered mentation, and disturbed coagulation(Todd *et al*.,2019). The causes of ALF are numerous, but the most common are acetaminophen (APAP) hepatotoxicity, non-APAP drug-induced liver injury (DILI), viral hepatitis, various genetic liver diseases, and autoimmune hepatitis. Oxidative stress is thought to occur in several of these conditions(Mitchell *et al*.,2015).The focus of this study is on the role of oxidative stress in the causes and progression of idiopathic acute liver failure. Oxidative stress (OS) is defined as an imbalance between oxidants and antioxidants accompanied by overproduction of reactive oxygen species (ROS)(Sies *et al*.,2017).Reactive oxygen species degrade polyunsaturated lipids, forming malondialdehyde. This compound is a reactive aldehyde and is one of the many reactive electrophile species that cause toxic stress in cells and form covalent protein adducts referred to as advanced lipoxidation end-products, in analogy to advanced glycation end-products. The production of this aldehyde is used as a biomarker to measure the level of oxidative stress in an organism (Hadeel *et al*., 2018; Rawaa *et al*., 2017). Oxidative stress results in the production of oxidation products and the depletion of endogenous antioxidants. Excessive ROS damage cellular structures and macromolecules, leading to cellular dysfunction and ultimately cell death (Finkel and Holbrook,2000). Consequent to tissue damage and cell death,IL-33 is released. Interleukin-33 (IL-33), a new member of the IL-1 family, induced the production of pro-inflammatory and T helper-2 (Th2)-associated cytokines. ST2 was to weaken Th2 inflammatory responses as its receptor [1].Serum levels of IL-33 and soluble ST2 elevated in liver failure, which could be a sign of immune hyperactivation, and/or a mechanism to down-regulate inflammation (Roth *et al*., 2010; Shu-Ling *et al*., 2016). The current study was designed to shed a light on association between serumIL-33 with oxidant- antioxidant status in patients liver failure. Alsoto evaluate a possible association between these parameters and to Investigation of the prognostic role of interleukin-33 in liver failure disease by using the ROC

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curve. Identification of such markers could also assist in identification of patients at increased risk for progression liver failure.

II. Materials and Methods

This study includes 60 subjects(30 patients and 30 controls((were 17 men and 13 female)). Sample size was determined according to the equation ofStephenThompson.Patients were randomly selected among those registered at AL-Hussein Teaching Hospital in Thi- Qar governorate.Duringthe period of 2021- 2022. Patients and controlsaged 30- 55 years and were presented with liver complaints, including yellowing of skin and eyes, abdominal pain and swelling, nausea, vomiting, dark urine colorand a general sense of feeling unwell. The exclusion criteria were known cases of liver failure induced by drug, patient's consumption an alcoholic, kidney disease, heart disease. Written informed consent was obtained from the participants ,The study protocol was assessed and approved by the Ethics Committee of our institution ,The research protocol did not interfere with any medical recommendations or prescriptions.

A.Samples Collection and Laboratory Tests

Aquantity of5 mL-blood sample was taken from eachparticipants (controls and patients .Samples were allowed to.coagulate at room. temperature in empty disposable tubes, then samples were centrifuged at 3000 xg for 10 minutes. Serum samples were .separated and stored at (-20 ° C) for subsequent measurement of biochemical parameters, unless used immediately.All patients were evaluated for serum IL-33, IL-23, NO, MDA, Cp and other routine laboratory tests such as AST, ALT, ALP, albuminand TB. Serum levels ofIL-33 and IL-23 were measured using enzyme-linked immunosorbent assay (ELISA), NO was determine .according to the method of (Dervisevic *et al*.,2012), MDA was determine .according to the method of Muslih *et al*.,2002) and Cp was determine .according to the method of Menden *et al*.,1977).

B. Statistical Analysis

Data was analyzed using SPSS software version 23.0. The results were expressed as mean±SD. Independent sample t test was applied to compare between parameters in all studied groups P-values (P≤0.05) were considered.The association between variables was assessed using Pearson's correlation, also used receiver operating characteristics curve (ROC) analysis.

III. Result

Of the patients, 17 (56.7 %) were men with a mean age of 44.22 years and 13 (43.3 %) women with a mean age of 46.32 years. without significant difference in each (age and sex).

Table1 shows the essential routine clinical examination. A significant increase was found in the concentration of serum (AST, ALT, ALPand total bilirubin) in patients group in comparison with controls group(P<0.001).These parameters have been demonstrated to be straightforward indicators for assessing the severity and outcome of liver failure patients. The majorities of these prognostic indicators, however, are focused on decreased liver function and have a high specificity but low sensitivity. As a result, we pondered if a marker reflecting illness etiology and assessing severity might be developed.

Table 1: levels of AST, ALT, ALP and TB in patients and controls groups

Parameters / Groups	Patients (Mean±SD) (N=30)	Controls (Mean±SD) (N=30)	p-value
AST (U/L)	194.90±31.78	30.15±3.22	<0.001
ALT (U/L)	132.45±28.81	23.27±3.21	<0.001
ALP (U/L)	361.50±23.34	72.81± 9.99	<0.001
Total bilirubin (mg/dL)	11.17±1.74	0.85± 0.23	<0.001

Table 2 shows the oxidant- antioxidant status levels. It was found that there is a significant increase in the concentration of serum (MDA, NOand CP) in patients group in comparison with thecontrols group(P<0.001).Furthermore, it was foundthat there is a significant increase in the concentration of serum (CP) in patients group in comparison with controls group(P= 0.002).

On the other hand it was foundthat there isasignificantdecrease in theconcentration of serum albumin in patients group in comparison with controls group (P= 0.009). These results confirm that markers of oxidative stress are potential new markers for the risk assessment of acute liver failure.

Table 2: levels of Albumin, MDA, NO and Cp in patients and controls groups

Parameters / Groups	Patients (Mean±SD) (N=30)	Controls (Mean±SD) (N=30)	p-value
Albumin (g/dL)	3.43.45±0.28	4.46±0.36	0.002
MDA (µmol/L)	5.51±1.2	1.44±0.31	<0.001
NO (µmol/mL)	13.42±2.14	6.40±1.3	<0.001
Cp (mg/L)	4.20±0.89	2.63±0.48	0.009

WhereNO:nitric oxide, MDA: malondialdehyde, Cp: Ceruloplasmin

Table3shows IL-33 and IL-23 levels. It was found that there is a significant increase in the concentration of serum (IL-33and IL-23) in patients group in comparison withthe controls group(P<0.001). This can be explainedas , in patients with liver failure, oxidative stress increases, causing cell death and, as a consequence, IL-33 is released.

Table 3: levels of IL-23 and IL-33 in patients and controls groups

Parameters / Groups	Patients (Mean±SD) (Number=30)	Controls (Mean±SD) (Number= 30)	p-value
IL-23 (pg/mL)	737.05±119.20	150.00±27.89	<0.001
IL-33 (pg/mL)	79.65±9.00	8.81±2.05	<0.001

Pearson's correlation was applied to explain the correlation among IL-33 and oxidative stress.Table 4and figures (1, 2, 3, 4 and 5)show that there is a positive correlation among IL-33 and (IL-23, MDA, NO and CP). However,itwas found that there is a negative correlation among IL-33 and albumin.

Table 4: correlation among IL-33, IL-23 and oxidative stress.

IL-33 with	r	p-value	Result
IL-23	0.402	0.079	Insignificant positive correlation
MDA	0.515	0.020	Significant positive correlation
NO	0.651	0.002	Significant positive correlation
CP	0.440	0.040	Significant positive correlation
Albumin	- 0.412	0.071	Insignificant negative correlation

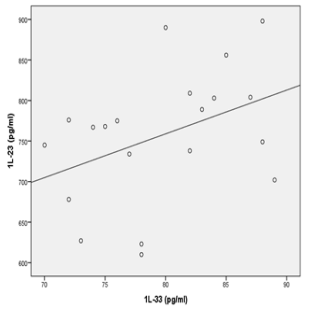


Figure 1 show the positive correlation between IL-33 and IL-23

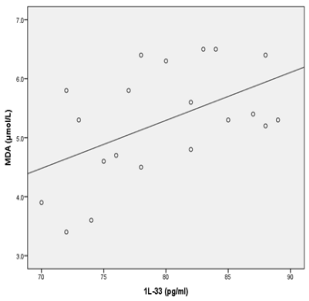


Figure 2 show the positive correlation between IL-33 and MDA

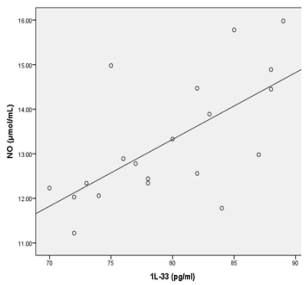


Figure 3 show the positive correlation between IL-33 and NO

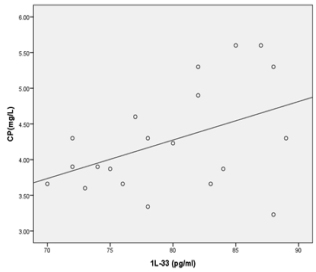


Figure 4 show the positive correlation between IL-33 and Cp

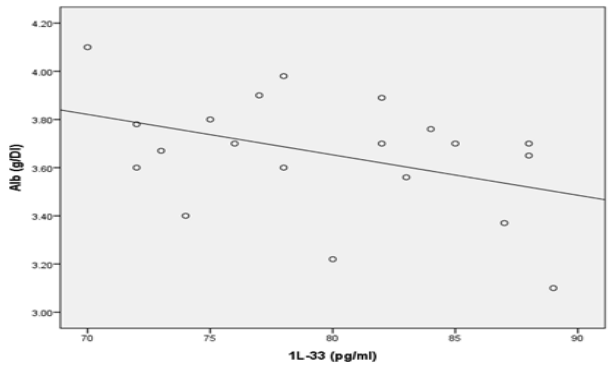


Figure 5 show the negative correlation between IL-33 and albumin

Receiver operating characteristics curve (ROC) analysis has been used to measure how well medical diagnostic procedures (or systems) can distinguish between two patient conditions, commonly referred to as "'diseased" and "non-diseased". The concept of a "separator" scale, on which the outcomes for the diseased and un-diseased form a pair of alternating distributions, is the foundation of a ROC curve. The details of ROC were given in Table (5) and Figure (6). Parameters tested had some validity for predicting acute liver failure, if the test value is greater than the Table value (0.5); it is possible to say that the hypothesis AUC result is significant. In this context, the AUC values together with the other parameters were given in Table (5).

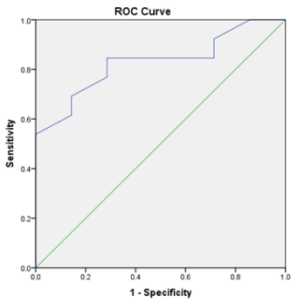
The ROC curve demonstrated that the levels of (IL-33, IL-23, MDA, NO and CP) have exhibited as good method for discriminating' between healthy individuals and patients with acute liver failure.The values were shown as follows:[(AUC = 0.830 ; 95% Confidence Interval (CI): 0.649 to 1.00 and SE: 0.092) (Figure 6 A)., (AUC = 0.667 ; 95% Confidence Interval (CI): 0.431 to 0.902 and SE: 0.120) (Figure 6B)..,(AUC = 0.827 ; 95% Confidence Interval (CI): 0.616 to 1.00and SE: 0.108) (Figure 6C)., (AUC = 0.804 ; 95% Confidence Interval (CI): 0.543 to 1.00 and SE: 0.133) (Figure 6D)., (AUC = 0.708 ; 95% Confidence Interval (CI): 0.472 to 0.945 and SE: 0.121) (Figure 6 E). Therefore, it is possible to state that these parameters may be definitely functional for the diagnosis of acute liver failure disease .Finally albumin showed a low validity to predict acute liver failure. (AUC = 0.411 ; 95% Confidence Interval (CI): 0.093 to 723 and SE: 0.162) (Figure6F).

Table 5: Area under the ROC curve for all analyzed biomarkers.

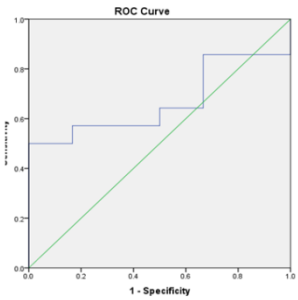
[Test Result Variable(s)]	[Area]	[Std. Error[a]]	[Asymptotic Sig.[b]]	[Asymptotic 95% Confidence Interval]	
				[Lower Bound]	[Upper Bound]
IL-33	0.830	0.092	0.017	0.649	1.000
IL-23	0.667	0.120	0.248	0.431	0.902
MDA	0.827	0.108	0.023	0.616	1.000
NO	0.804	0.133	0.035	0.543	1.000
CP	0.708	0.121	0.149	0.472	0.945
Albumin	0.411	0.162	0.536	0.093	0.723

a. Under the nonparametric assumption

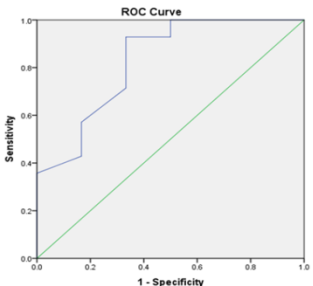
b. Null hypothesis: true area = 0.5

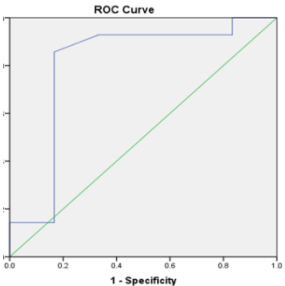


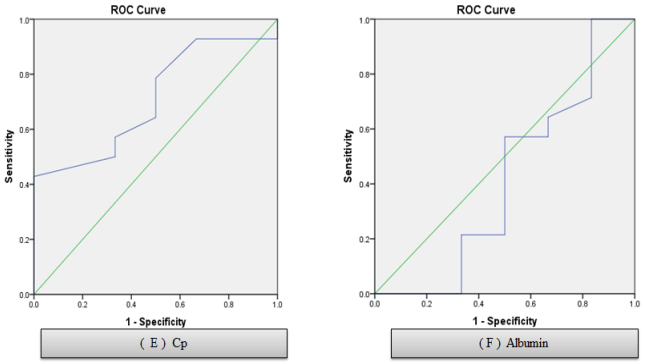
(A) IL-33



(B) IL-23







analyzed biomarkers.

Figure 6(A,B,C,D,E And F): the ROC curve for all

IV. Discussion

In this study, the role of IL-33 and its relationship with oxidant-antioxidants Status in patients with liver failure without any external risk factor such as alcohol consumption or drugswas investigated . Many human diseases, including acute liver failure, are associated with inflammation. These diseases are characterized bythe excessive of ROS production. Dysfunctional mitochondria have also been implicated in these disorders, since they act as both a source and a target of ROS(Zhen Tian *et al*.,2018). Studies have suggested that, in hepatocytes, reactive oxygen species (ROS) play important roles in the pathophysiology of acute liver failure; injured/dead hepatocytes greatly increase oxidative stress during acute liver failure, which in turn contribute to further hepatocyte loss and impede regeneration, culminating in a vicious cycle(Torres *et al*.,2019). Autophagy is an intracellular recycling mechanism that helps to maintain cellular homeostasis and regulates the cellular adaptive response during stressful situations (Klionsky *et al*.,2021). Autophagy has been implicated in the regulation of resident liver cells, including hepatocytes, hepatic stellate cells (HSCs) and macrophages(Shen *et al*.,2020). Although the link between autophagy and cell death is complicated, a growing body of evidence suggests that autophagy enhances cell longevity by removing reactive oxygen species (ROS). Nitric oxide (NO) accelerates Hepatic stellate cells death by generating ROS(Brenner *et al*.,2013). The cause of many clinical issues linked with liver failure is severe peripheral and splanchnic vasodilation, which is a key hallmark of individuals with liver failure. Hepatocytes, Kupffer cells, HSCs, and hepatic sinusoidal endothelial cells (SECs) may all create NO, a gaseous chemical with significant vasodilator effects. NO synthase (NOS) employs a system of redox processes to produce NO (Wang *et al*., 2018; Ruart *et al.* ,2019).Endogenous NO has a very short half-life after being synthesized by NOS, about 1 second. As a result, NOS controls endogenous NO levels (Förstermann and v,2012). NO may play a role in ACLF according to several recent studies. During acute liver failure, NO inhibits autophagy in Hepatic stellate cells, promoting cell death (Jin et al.,2017).and autophagy deficit in Sinusoidal endothelial cells reduces intrahepatic NO bioavailability owing to both decreased production and increased scavenging, impairing the antioxidant response (Ruart et al.,2019; Fei Wang *et al*., 2022).During liver inflammation, IL-33 is released after liver cell death (Arshad *et al*., 2011). The IL-33 plays a key role in several diseases, including hepatitis(Gregory *et al*., 2016). Liver endothelial cells constitutively express IL-33, and it was shown IL-33 to be overexpressed in hepatocytes during necrotic NKT-TRAIL-mediated hepatic cell death(Arshad *et al*.,2011; Arshad *et al*.,2012) and viral hepatitis (Arshad *et al*.,2013). IL-33 is also produced by the hepatic stellate cells in hepatic fibrosis (Marvie et al.,2010). Thus, during liver inflammation, IL-33 is released after liver cell death (Arshad *et al*.,2011), and it was considered to act as an "alarmin," like high-motility group box protein 1 and IL-1α (Haraldsen et al.,2009). However, the effects of endogenous IL-33 during liver inflammation remain obscure, and the ST2+ liver immune cells and the effects of IL-33 on these target cells have yet to be characterized Gregory et al.,2016).More recent findings suggest that IL-33 is specifically released during necrotic cell death associated with tissue damage and is now referred to as one of the ''alarmins''. Extracellular IL-33 may engage the ST2 receptor on immune cells to promote the initiation of healing responses(Vladislav *etal*.,2012). Liver inflammation rapidly leads to the production of copious amounts of IL-33 by hepatocytes and liver endothelial cells (lee *et al*.,2012)). Therefore, IL-33 has been proposed to function as an alarmin to alert the immune system of tissue damage following infection. Evidence suggests that when acute and massive liver damage occurs, the release of IL-33 by injured hepatocytes might be a protective mechanism, while in chronic injury, IL-33 plays the role of a hepatic fibrosis-enhancing factor. Thus, it is necessary to judge and weigh the opposing functions of IL-33 before clinical application(Zijian et al.,2017; Weiskirchen andTacke,2017). According to the present study it was found significant increase in the concentration of serum IL-23. IL-23 production has been shown in prevousestudyes to be involved in acetaminophen overdose-associated hepatitis,additionally, the presence of the hepatitis B virus is known to induce IL-23 production from myeloid dendritic cells and macrophages and lead to Th17 differentiation and liver damage through the IL-17 receptor present on stellate cells and mouse dendritic cells in the liver (John *et al.*,2018). But in this study, samples were taken from patients who do not take medications also do not have a history of liver disease. The increase may be due to oxidative stress because since its discovery has been identified as a proinflammatory cytokine.

This study has some limitations, such as the relatively low number of patients,disease rarity. Also may be some patients have a history of liver disease ortakemedications. Moreover, the molecular mechanism by which serum IL-23 is involved in the progression of acute liver failure is not completely clear. Nevertheless, the present article is the first report to demonstrate the positive correlation between IL-33 and oxidative stress. Also this study demonstrates that serum IL-33 could serve as a promising predictor of diagnostic acute liver failure. Our findings could be used to enhance the diagnostic accuracy of the Model for early - stage liver disease. Score as a non-invasive biomarker with great clinical significance.

Conclusion

Our findings indicated that there is anassociation between abnormal serum IL-33 levels and Oxidant-Antioxidants Status. Although the etiology of relatively not well-established, it was recommend serum IL-33 level monitoring in all patients. The use of ROC curve analysis confirmed thatIL-33 is effective for the diagnosis of liver failure. so the level of IL-33 is a significant feature of the monitor disease progression early.

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