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High Serum Interlukin-6 in Acute on Chronic Liver Failure (ACLF) is a Early Mortality Predictor

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Abstract:

Background and objectives: Acute-on-chronic liver failure (ACLF) is characterised by a poor prognosis. Interleukin-6 (IL-6) is a pro-inflammatory cytokine associated with both severe liver damage and the liver regeneration, suggesting that systemic inflammation plays a substantial role in its aetiology. There is no research on how serum IL-6 affects ACLF prognosis. To examine serum IL 6 levels as a separate predictor of early mortality in ACLF patients.

Method: A retrospective analysis was conducted at NIMS Jaipur from December 2021 to June 2023. In this study 150 patients participated and IL 6 serum levels were measured. The results were examined in relation to mortality, baseline serum IL-6 levels, and dynamic changes in IL-6 levels over the course.

Results: Mortality was linked to the level of IL-6 in the serum. In contrast to living patients, higher mortality rates within 4 weeks were seen in patients with high IL-6 levels > 19.8 pg /mL (7.3 -57.6) compared to low IL-6 levels 12.5 (4.7- 22.3) p=0.018 pg/mL Odds ratios were estimated using univariate and multivariate logistic regression, and the results were 2.20 (95% confidence interval [CI] and 2.12 (95%CI) respectively. In comparison to patients with high IL-6 levels at 4 weeks, those with high IL-6 levels between weeks 5 and 8 had a mortality rate of 15.0%, which was considerably greater than 6.6% in low IL6. The dynamic change of increasing trend of IL-6 significantly high mortality rate.

Conclusion: In patients with ACLF, the sustained high serum IL-6 level is a stand-alone risk factor for high mortality.

Keywords: ACLF, IL-6, renal dysfunction, APACHE, Mortality.

Introduction

Acute-on-chronic liver failure (ACLF) describes a rapidly worsening chronic liver condition. The rapid decline into multi-organ failure carries with it a high risk of death within a very short amount of time (28 days) [1,2,3]. The type of acute insult specifically hepatic or extrahepatic, the stage of liver disease with cirrhosis or chronic hepatitis and the concomitant organ failure(s) that should be considered in the definition of ACLF. Therefore, different prognostic scores have been proposed and validated on severity criteria [4]. There was a two-day meeting in October 2018 at New Delhi with finalization of the new AARC consensus. The consensus definition of liver disease published by the European Association for the Study of Liver Disease- Chronic Liver Failure[5] (EASL-CLIF) and the North American Consortium for the Study of End stage Liver Diseases (NACSELD) criteria is generally accepted in the absence of a universally accepted definition. EASL-CLIF grade 1-3 but of these only 15.3% had ACLF by NACSELD.Commonly, doctors will refer to the underlying cause of ACLF as a "state of Immune dysfunction." Identifying patients with a likelihood of 28-day mortality is an important part of clinical practise, as it allows prioritisation of the need for an urgent liver transplant and prompt treatment. In the EASL-CLIF acute-on-chronic liver failure in cirrhosis (CANONIC) study, including Child-Turcotte-Pugh (CTP), Model for End-Stage Liver Disease (MELD), Acute Physiology and Chronic Health Evaluation (APACHE)4, Sequential Organ Failure Assessment (SOFA), and CLIFSOFA grading all were examined. In spite of this, no single source could settle the debate Recently, the American Association for the Study of Liver Disease and the European Association for the Study of the Liver created a research consortium to advance the state of the science of acute-on-chronic liver failure. [4,5]. The goal of this consortium is aimed at improving outcomes, identification of a subset of patients with cirrhosis at high risk for

deterioration, and the inciting events that lead to this deterioration. Liver transplant remains the only curative option for advanced cirrhosis. [6] Heavy alcohol consumption is the most common etiology of acute-on-chronic liver failure. In some patients, ACLF is associated with a fatal outcome in less than 6 months. We evaluated the prognosis of patients with alcohol-related ACLF in our cohort and explored the prognostic factors. [7]

Recent research has shown that IL-6 controls several metabolic processes, including as glucose absorption, glycolysis, fatty acid oxidation, and oxidative phosphorylation. Additionally, it has been discovered that various virus-related disorders have much higher levels of IL-6 expression and release, and that this increase is directly connected with the severity of the disease. In this study, we provide an overview of how IL-6 regulates immune-metabolism in a few illnesses linked to viral infection. These viruses' taxonomy and modes of transmission share several characteristics in common. Among these, non-infective alcoholic hepatitis and others, hepatitis B virus (HBV), human cytomegalovirus (HCMV), adenovirus (AdV), and dengue viruses (DV) are DNA viruses, whereas severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), human immunodeficiency virus (HIV), and enterovirus 71 (EV71) are RNA viruses. All three HBV, HIV, and HCMV infections can be passed from mother to child, through the blood, or through sexual contact. Conversely, DV is spread through mosquito bites, but SARS-CoV-2, AdV, and EV71 can all spread through the digestive tract, respiratory tract, and direct contact. The target role of IL-6 in tying various viruses, immunity, and metabolism can be better understood by analysing and contrasting its role in similar or unlike forms of viral infections. [8,9, 10].

Jaundice (serum bilirubin > 5 mg/dl) is a hallmark symptom of acute hepatic failure (ACLF). Chronic alcoholic hepatitis, Inflammatory thrombocytopenia (international normalised ratio [INR] > 1.5 or prothrombin activity 40%). Within 4 weeks of symptom onset, a diagnosis of ascites and/or encephalopathy was made, Cirrhosis or chronic liver disease without a history of such a diagnosis. There is an increase in mortality after 28 days due to this. Types A and B (compensated) cirrhosis and type C & D (decompensated) cirrhosis have been identified [11,12,13].

Materials and Method

This was a retrospective observational study conducted from December 2021 to June 2023, in the department of Gastroenterology, at National Institute of Medical Sciences Hospital Jaipur, Rajasthan, India. In the study total 150 individuals (65 Alcoholics and 85 non- alcoholic patients) were included in the study, after following inclusion and exclusion criteria bellow and after getting informed consent from patients and approved by institutional ethical committee.

Inclusion criteria:

- Age (16-70 years)
- Chronic liver disease – Alcohol, Hepatitis-b, Hepatitis-c, NASH/MAFLD, Cryptogenic, and Autoimmune causes.
- Patients with COVID -19 RT-PCR negative

Exclusion criteria:

- The pediatric age range
- Metabolic illnesses such as hemochromatosis, Alpha 1 antitrypsin deficiency, and Wilson's disease are not taken into study group.

Method

- 150 patients visited to gastroenterology OPD among which serum IL 6 levels were measured with the help of ADVIA Centre assay, which is fully automatized, one step direct immunoassay using chemiluminescent technology.
- Both ACLF and chronic liver disease brought on by HBV infection and alcohol consumption were used to support the diagnosis of ACLF.
- The patients visited OPD of Gastro department and diagnosis of ACLF was made in accordance with the diagnostic and treatment recommendations for liver failure.
- Within 4 weeks, ACLF emerges as the major clinical sign of acute hepatic Decompensation caused by underlying chronic liver disease. Diagnostic criteria included the presence of ascites and/or hepatic encephalopathy on physical examination and/or jaundice (serum bilirubin 5 mg/dL (85 mol/L)), coagulopathy (international normalised ratio [INR] 1.5 or prothrombin activity 40% and/or coagulopathy
- A persistent infection was diagnosed when HBsAg was positive.

Statistical Analysis

Collected data were entered in Microsoft excel 2016 for further statistical analysis. Categorical data were expressed in terms of frequency and proportion, while quantitative data were expressed in terms of mean and standard deviation. Mean difference in the different variables between survival and non-survival and High and low level of IL-6 values were analyzed with the help of t-test. Binary logistic regression with forward elimination was used to evaluate factors related to prognosis. The choice of variables for the multivariable analysis was based on the results of univariable analysis and clinical correlation. The Cox proportional hazards regression was used for group comparisons of mortality between 5 and 8 weeks p-value<0.05

considered as statistically significant at 5% level of significance.

Observation and Result

Table 1 shows mean age difference and gender difference between survival and non-survival patients, and mean age was statistically significant between the groups, mean age in non-survival group was more compared to survival group.

The 2 table shows, mean difference of various lab parameter between survival and non-survival patients, mean difference of albumin, bilirubin, creatinine level, INR, MELD score, HE, UGB, SGB, Hyponatremia, Renal Dysfunction and IL-6 showed significant difference between the groups (P-value<0.05)

Table 1: Demographic profile of study population between survival and non-survival.

Parameters	All patients (n = 150)	Surviving patients (n=125)	Deceased patients (n =25)	P value
Age (yr)	42.9 ± 11.4	42.8 ± 10.7	48.7 ± 10.5	0.0126
Male, n (%)	100 (66.6)	85 (68)	15 (60)	0.264

Serum creatinine level ranging from 1.5 to 1.9 mg/dL. P values shown in bold indicate statistical significance. ALT: Alanine transaminase; AST: Aspartate transaminase; GGT: γ-glutamyl transferase; INR: International normalized ratio; WBC: White blood cell count; MELD: Model for End-stage Liver Disease; HE: Hepatic encephalopathy; UGB: Upper gastrointestinal bleeding; SBP: Spontaneous bacterial peritonitis; IL-6: Interleu**kin-**6 Student's t-tests for pairwise comparisons of parametric data distributions**.**

Table 2: Distribution of Laboratorial parameters between survival and non-survival.

Parameters	All patients (n = 150)	Surviving patients (n=125)	Deceased patients (n =25)	P value
Albumin (g/L)	30.9 ± 13.5	30.7 ± 5.3	32.6 ± 6.4	<0.001
Globulin (g/L)	27.8 ± 9.2	28.7 ± 8.8	29.3 ± 9.5	0.759
Bilirubin (mg/dL)	17.8 ± 7.8	18.5 ± 8.2	23.5 ± 8.2	0.0064
ALT (U/L)	140	150	175	0.255
AST (U/L)	151	142	179	0.1
GGT (U/L)	70	67	59	0.226
Creatinine (μ mol/L)	74.3 ± 27.8	70.7 ± 22.8	87.2 ± 42.9	0.006
INR	3.4 ± 0.7	3.8 ± 0.8	5 ± 0.9	<0.001
WBC (× 109/L)	6.5 ± 4.6	8.2 ± 4.5	9.0 ± 5.2	0.4307
Hemoglobin (g/L)	115 ± 24	117 ± 23	111 ± 30	0.261
Platelet count (× 109/L)	89 ± 46	92 ± 44	88 ± 55	0.6918
HBV DNA (log10 IU/mL)	4.2 ± 1.4	3.1 ± 2.4	3.5 ± 3.4	0.4817
MELD	29.5 ± 4.8	26.7 ± 5.2	29.8 ± 4.6	0.0063
HE, n (%)	60 (40.6)	42 (33.3)	23 (92)	< 0.001
UGB, n (%)	11 (7.3)	8 (6.4)	6 (24)	0.0057
SBP, n (%)	61 (40.6)	46 (36.8)	23 (92)	<0.001
Infection excluding SBP, n (%)	74 (49.3)	44 (35.2)	11 (44)	0.404
Hyponatremia, n(%)	67 (44.6)	38 (30.4)	21 (84)	<0.001
Renal dysfunction, n (%)	19 (12.6)	9 (7.2)	11 (44)	<0.001
IL-6 (pg/mL)	13.6	12.5	19.8	0.011

Table 3: Demographic profile of study population between low and high IL-6

Parameter	High IL-6 level (n= 61)	Low IL-6 level (n= 54)	P value
Age (yr)	42.9 ± 11.9	42.8 ± 10.7	0.963
Male, n (%)	34 (55.7%)	27 (50%)	0.538

Table 4: Distribution of Laboratorial parameters between low and high IL-6

Parameter	High IL-6 level (n= 61)	Low IL-6 level (n= 54)	P value
Albumin (g/L)	27.7 ± 5.8	33.1 ± 17.7	0.0263
Globulin (g/L)	28.9 ± 9.4	28.3 ± 9.7	0.7371
Bilirubin (mg/dL)	22.0 ± 9.2	18.4 ± 8.9	0.0425
ALT (U/L)	113	163	0.071
AST (U/L)	144	165	0.133
GGT (U/L)	65	75	0.019
Creatinine (µ mol/L)	75.8 ± 27.8	71.5 ± 23.7	0.377
INR	3.4 ± 0.7	2.5 ± 0.7	<0.001
WBC (× 109/L)	8.4 ± 4.7	8.1 ± 3.8	0.7096
Hemoglobin (g/L)	112 ± 24	115 ± 24	0.5049
Platelet count (× 109/L)	86 ± 48	92 ± 43	0.4839
HBVDNA (log10 IU/mL)	4.2 ± 2.5	3.5 ± 3.3	0.1995
MELD	25.7 ± 4.7	25.3 ± 5.5	0.6446
HE, n (%)	26 (42.62)	22 (40.7)	0.838
UGB, n (%)	9 (14.7)	4 (7.4)	0.214
SBP, n (%)	55 (90.1)	51 (94.4)	0.393
Infection excluding SBP, n (%)	44 (72.1)	41 (75.9)	0.643
Hyponatremia, n (%)	57 (93.4)	50 (92.5)	0.858
Renal disfunction, n (%)	9 (14.7)	4 (7.4)	0.214
Mortality, n (%)	12 (19.6)	10 (18.5)	0.875

Table 5: Risk factors affecting individuals with acute on chronic liver failure's prognosis

Parameter	First step			Last step		
	OR	95%CI	Pvalue	OR	95%CI	Pvalue
Age, (years)	1.05	1.02-1.05	0.007	1.05	1.01-1.08	0.009
Bilirubin,(mg/dL)	1.05	1.03-1.09	0.002	1.05	1.002-1.08	0.037
Albumin (g/L)	1.02	0.99-1.03	0.34	-	-	-
Creatinine,(µmol/L)	1.03	1.02-1.04	<0.001	1.02	1.01-1.05	0.001
INR, (iu)	3.47	2.29-6.27	<0.001	3.55	2.18-5.74	<0.001
ALT,(U/L)	1.01	1.00-1.00	0.198	-	-	-
AST, (U/L)	1.01	1.00-1.00	0.094	-	-	-
GGT(U/L)	1.01	0.98-1.00	0.134	-	-	-
Hemoglobin, (g/L)	0.99	0.98-1.00	0.042	-	-	-
HE(yes/ no)	3.93	1.59-6.42	0.002	2.48	1.22-6.31	0.022
UGB (yes/ no)	6.55	1.55-17.69	0.005	4.74	1.03-22.90	0.048
Hyponatremia (yes/ no)	2.39	0.98-1.91	0.058	-	-	-
Renal dysfunction (yes/ no)	7.35	2.54-21.33	<0.001	-	-	-
IL-6,pg/ml (>11.8vs≤11.8)	2.2	2.27-2.52	0.004	2.12	1.16-3.89	0.018

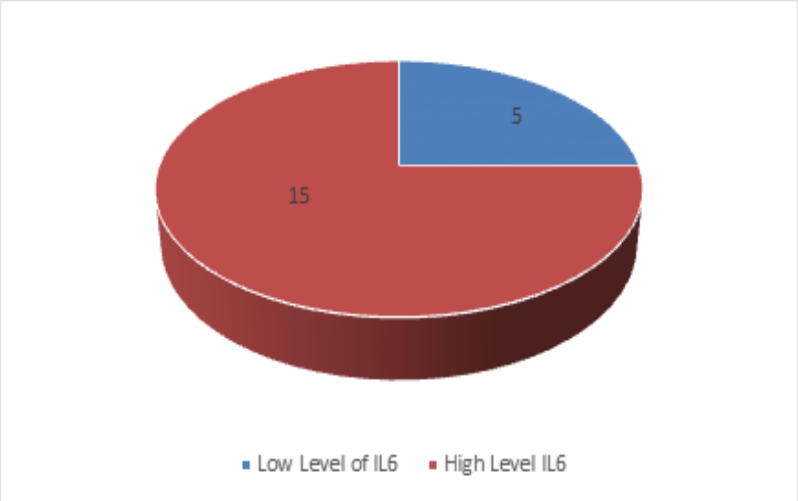

Figure 1. Comparison of mortality with level of IL-6

Table 6: Mortality and dynamic changes in interleukin 6 at 5 Week

Mortality	Frequency	HR (95%CI)	P-value	P value for trend
Group A (n = 59)	2 (3.38%)	1		0.024
Group B (n=105)	6 (5.71%)	1.54	0.528	
Group C (n=25)	3(12%)	2.4	0.281	
Group D (n =53)	9(17%)	2.84	0.136	

Patients deceased had higher levels of IL-6 than those who survived 17.9 (7.3-57.6) vs. 10.4 (4.7-22.3), P = 0.011; they also had higher levels of bilirubin, creatinine, white blood cell count (WBC), INR, and MELD score 27.8 4.5 vs. 23.6 4.2; P <0.001). In addition, patients deceased were older than those who survived (47.6 10.2 vs. 43.9 10.6, P = 0.007).

The multivariate model included variables such as IL-6, age, bilirubin, creatinine, INR, haemoglobin, as well as the existence of HE, UGB, and renal failure that were substantially different between living patients and those who passed away in univariate analysis. Age (odds ratio [OR] = 1.05, 95% confidence interval [CI]: 1.01-1.08, P = 0.009), bilirubin (OR = 1.05, 95%CI: 1.03-1.09, P = 0.037), creatinine (OR = 1.03, 95%CI: 1.02-1.04, P = 0.001), INR (OR = 3.47, 95%CI: 2.29-6.27, P 0.001), presence of HE

In comparison to patients with low levels of IL-6, patients with high levels of IL-6 had a significantly higher 4-week mortality rate (P = 0.036). Patients with HBV-ACLF had a higher death rate between weeks 5 and 8 when their IL-6 levels were high at 4 weeks (P = 0.037).

Patients were categorised into four groups (A, B, C, and D) based on the dynamic changes in IL-6 over the course of four weeks: Patients with high IL-6 levels at baseline and low IL-6 levels at four weeks, low IL-6 levels at baseline and high IL-6 levels at four weeks, and high IL-6 levels both at baseline and at four weeks. 3.38%, 5.71%, 12%, and 17% of those in groups A, B, and C respectively experienced mortality. The dynamic change in mortality was significantly different in each of the four groups (P = 0.024).

Discussion

In our 150 retrospective study population, we found that IL-6 was a distinct factor that predicted the prognosis of ACLF of any cause who died at 4 weeks had higher baseline levels of IL-6 than survivors 19.8pg/ml vs 12.5pg/ml. Similar study was done by Chao Zhou et al Their findings were correlating with my findings The serum IL-6 level was associated with mortality. Within 4 week, deceased patients had significantly higher levels of IL-6 at baseline than surviving patients [17.9 *vs* 10.4) [14]

The odds ratio(OR) calculated using univariate and multivariate logistic regression were 3.55(95% confidence interval (CI)2.18-5.74 Pvalue=<0.001, it is with same study of Chao Zhou et al The odds ratios calculated using univariate and multivariate logistic regression were 2.10 (95% confidence interval [CI]: 1.26-3.51, *P* = 0.005) and 2.11 (95%CI: 1.15-3.90, *P* = 0.017), respectively [14].

In our study the mortality in patients with high IL6 at 4 weeks was 15% (24.59)higher than the patients with low IL6 at 4 weeks was 5(9.25) with hazards ratio=2.48, 95% CI1.16-3.89 P value 0.018 . Similar findings in study ofChao Zhou et alThe mortality between weeks 5 and 8 in patients with high IL-6 levels at 4 week was 15.0%, which was significantly higher than the 6.6% mortality rate in patients with low IL-6 levels at 4 week (hazard ratio = 2.39, 95%CI: 1.05-5.41, *P* = 0.037). [14] The increasing trend of the mortality rate with the dynamic changes of IL-6 was significant (*P* for trend = 0.023).

In our study 1st table shows the significance of p=values for albumin(<0.001), bilirubin (0.0064), creatinine (0.006), INR 5 (<0.001), MELD 29.8 (0.0063), HE 23 (<0.001), UGB 11(0.0057), SBG 61 (<0.001)) Hyponatremia 67(<0,001) Renal dysfunction 19 (<0.001) and IL-6 19.8pg/ml.Multivariate analysis identified IL-6 > 23.3 pg/mL at admission and model for end-stage liver disease (MELD) score ≥ 25 on day 4 of admission as significant independent factors for mortality within 6 months. [7]

Data from the first , second and four weeks of therapy showed that patients with high IL-6 levels died has twice the mortality as individuals with low IL-6 levels. The results suggested that dynamic alterations and IL-6 could be used as supplementary prognostic indicators for ACLF patients' outcomes. The first stage in the production of acute-phase proteins is the release of IL-6, which is carried out by monocytes, macrophages, T cells, fibroblasts, and endothelial cells. There is general consensus that increased IL-6 is a strongly pro-inflammatory cytokine that quickly primes the host immune system to carry out a variety of beneficial tasks. Under hetero-subtypic exposure, early and direct IL-6 signals facilitated infection-site immune responses. In our study CRP 87.2m,mol/L and WBC 9.0 (9.0x109/L).

According to several research, IL-6 rather than WBC or CRP is a better indicator of the degree of systemic inflammation among individuals with severe liver impairment. However, over time, the liver may suffer from high IL-6 levels. In our study

there was some variations in albumin, GGT and haemoglobin with on treatment. Similar findings were noted from the studies of Noor MK et al.,Remmler J at al. and Sarin SK et al.they found slight variations in albumin, GGT, and haemoglobin after the two dosages, our analysis discovered no correlation among both IL-6 doses and the MELD score, WBC count, existence of sequelae, or infections at various sites [15,16,17].

Possible explanations include IL-6's differential expression during the acute phase response and the chronic condition. The duration of the acute phase reaction is usually between 24 and 48 hours, although the infections reflected in our research were active beyond the acute phase. Furthermore, we believe this demonstrates that IL-6's prognostic impact is not restricted to cases of acute illness or death due to infection [18, 19]. The motivations behind this realisation remain unknown. The biological activity of the cytokine IL-6, which has various biological functions including inducing inflammatory responses and preserving tissue homeostasis, has been linked to liver regeneration in a laboratory model of acute liver failure. Interleukin-6 was also thought to have a role in the development of liver cancers. A complex role for IL-6 in the liver is class or transsignaling. Although further research is required in this area, targeted reduction of IL-6 transsignaling has showed promise in the treatment of liver problems [20, 21]. The pathophysiological distinctions among acute and chronic liver failure and the various long-term repercussions of IL-6 in our patients who have ongoing liver disorders may help to explain our conflicting findings in individuals with HBV ACLF. While persistent IL-6 spikes may harm the liver along with other organs, acute and brief rises in IL-6 levels might be helpful for liver regeneration. According to the results of our investigation, dynamic variations in IL-6 levels were associated with mortality. Patients who experienced dynamically elevated or sustained high IL-6 levels had a higher risk of passing away than those who experienced dynamically decreased or sustained low IL-6 levels. This finding indicated that the concentration of IL-6 and time played a role in the development of the disease. There are a number of constraints on this study [22,23]. The purpose of this retrospective study was to analyse IL-6's potential predictive value as a biomarker of inflammation. Since no correlation analysis was performed between procalcitonin or CRP and IL-6, these parameters were not analysed in this investigation; nonetheless, this had no influence on how IL-6 affected prognosis [24].

Not all participants had access to this information. In addition, the impact of IL-6 dynamic changes on mortality was not calculated for numerous people because they obtained negative findings from a second IL-6 test. We found no distinguishing characteristics or mortality rates among the 150 patients we analysed. However, we did examine the presence of infection, such as SBP, in individuals with varying IL-6 levels, albeit we did not distinguish between ACLF induced by infection and ACLF not caused by infection. Although IL6 was discovered to improve ACLF prognosis, the mechanism responsible for this improvement remains unknown and needs further study. Overall, our results demonstrate that IL-6 is a separate prognostic factor associated with ACLF prognosis. Predicting mortality in patients with ACLF may be possible with the use of IL-6. However, additional studies are needed to evaluate and confirm the prognostic importance of IL-6 [24, 25,26.]

Conclusion

Finally concluded that our observation showed that individuals with ACLF have a higher mortality risk when their serum IL-6 levels are high.

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