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A Study on Serum IL-6 Levels in Patients with Liver Cirrhosis of Any Cause and its Correlation with Child Pugh Score in Assessing the Disease Severity

Dr. Atul Choudhary[1], Dr. Swani Bhagat[2]

[1]MD Medicine, ASCOMS Jammu.
[2]MD Pathology, Government Medical College, Srinagar

Corresponding Author: Dr. Swani Bhagat

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ABSTRACT

Background: Liver cirrhosis is a chronic and progressive disease characterized by the development of fibrosis and distortion of the liver architecture. One potential biomarker that has gained attention in recent years is interleukin-6 (IL-6), a pro-inflammatory cytokine that plays a crucial role in the immune response and inflammatory processes. In the present study, serum IL-6 levels will be measured using enzyme-linked immunosorbent assay (ELISA) and correlated with the Child-Pugh score.

Methods: This study was a cross-sectional design conducted at ASCOMS Jammu from June 2021 to November 2021. Fifty patients who presented with symptoms of liver cirrhosis, such as abdominal pain, abdominal distention, jaundice, and reduced urine output, were randomly selected from the outpatient or emergency departments.

Results: The study analyzed data from 50 patients, finding that 6% were below the age of 30, 24% were between 30 and 40, and 70% were over 40. 94% of patients were male, while only 6% were female. The study found a significant increase in the mean portal vein diameter as the Child class increased, and a significant correlation between PT prolongation and mean IL-6 levels. However, there was no significant correlation between Child class and SAAG value.

Conclusion: The severity of varices in patients with liver cirrhosis was found to be strongly associated with the level of serum IL-6, suggesting that serum IL-6 can be used as a non-invasive way to identify varices in patients with liver cirrhosis, particularly when OGD scopy is not available or if the patient is too sick to be moved to the OGD room. Elevated levels of IL-6 have also been associated with hepatic encephalopathy, liver fibrosis, and cirrhosis.

Keywords: Interleukin 6, liver cirrhosis, hepatic encephalopathy, child Pugh score

INTRODUCTION

Liver cirrhosis is a chronic and progressive disease characterized by the development of fibrosis and distortion of the liver architecture. The most common causes of liver cirrhosis include chronic viral hepatitis, alcohol consumption, and non-alcoholic fatty liver disease. Despite advances in medical management, liver cirrhosis remains a significant health problem worldwide, with a high mortality rate and a considerable impact on healthcare resources. Child-Pugh score is a widely used clinical tool to assess liver function and predict survival in patients with cirrhosis. However, it has limitations and may not accurately reflect disease severity. Therefore, there is a need for biomarkers that can complement or improve the prognostic accuracy of the Child-Pugh score.[1] One potential biomarker that has gained attention

in recent years is interleukin-6 (IL-6), a pro-inflammatory cytokine that plays a crucial role in the immune response and inflammatory processes.[2] Interleukin-6 (IL-6) is synthesized at the site of inflammation and plays a pivotal role in the acute phase response, characterized by a diverse range of clinical and biological features, including the production of acute phase proteins. The combination of IL-6 with its soluble receptor sIL-6Rα facilitates the shift from acute to chronic inflammation by altering the nature of leucocyte infiltrate, transitioning from polymorphonuclear neutrophils to monocyte/macrophages. Furthermore, IL-6 exerts stimulatory effects on T- and B-cells, promoting chronic inflammatory responses. Approaches targeting IL-6 and its signaling pathways have demonstrated successful outcomes in preventing and treating models of chronic inflammatory disorders.[2] Several studies have investigated the association between serum IL-6 levels and the severity of liver cirrhosis. The results of these studies have been conflicting, with some showing a positive correlation between serum IL-6 levels and the Child-Pugh score, while others have reported no significant association.[3-5] In this context, the present study aims to investigate the correlation between serum IL-6 levels and Child-Pugh score in patients with liver cirrhosis of any cause and assess the utility of serum IL-6 levels as a biomarker for disease severity. The study will involve a cohort of patients with liver cirrhosis of any cause and various degrees of disease severity. Serum IL-6 levels will be measured using enzyme-linked immunosorbent assay (ELISA) and correlated with the Child-Pugh score. The findings of this study could provide important insights into the role of serum IL-6 levels as a biomarker for disease severity in patients with liver cirrhosis. It may also have implications for the clinical management and prognostic evaluation of patients with this debilitating disease.

METHODS

This study was a cross-sectional design conducted at ASCOMS Jammu from June 2021 to November 2021. Fifty patients who presented with symptoms of liver cirrhosis, such as abdominal pain, abdominal distention, jaundice, and reduced urine output, were randomly selected from the outpatient or emergency departments. Patients were excluded if they had co-morbidities such as connective tissue disorders, chronic inflammatory conditions, or malignancies, among others. A complete history was taken, and a physical examination was conducted with monitoring of vitals. A battery of blood investigations was done, including renal functions, liver functions test, complete blood count, ECG, HBs Ag, HIV, Anti HCV, prothrombin time, aPTT, urine analysis, lipid profile, serum IL-6, chest X-ray, USG abdomen, portal Doppler study, ascitic fluid analysis, and OGD scopy. Serum interleukin 6 (IL-6) levels were measured using an ELISA method with pyrogen/endotoxin-free collecting tubes. Pyrogen/endotoxin-free collecting tubes were used to collect the samples, which were carefully removed from the red cells after clotting. Centrifugation was performed at approximately 1000 x g for 10 minutes, and the serum was removed. To avoid repeated freeze-thaw cycles, samples were aliquoted (250-500µl) and stored frozen at –70°C. The IL-6 ELISA kit has a minimum detectable dose of less than 2pg/ml and recognizes both natural and recombinant human IL-6. Several proteins were tested for cross-reactivity, including IL-1a, IL-1b, IL-10, IL-12, IFN gamma, IL-4, TNF alpha, IL-8, and IL-13, and no cross-reactivity was observed. The intra-assay coefficient of variation was calculated to be 4.2%, and the inter-assay coefficient of variation was 7.7%. The immunoassay was calibrated against the International Reference Standard NIBSC 89/548, which is quantitated in International Units (IU), with 1IU corresponding to 11pg of

this given ELISA kit measurement of IL-6. The study inclusion criteria were recently diagnosed/known cases of cirrhosis of any cause, with or without portal hypertension, in the age group of 25-50 years. The exclusion criteria include cirrhosis with SBP, hypertensive patients, diabetic patients, dyslipidemic patients, connective tissue disorders, any chronic inflammatory condition, autoimmune liver diseases, malignancy/metastasis, haematological malignancy, known coronary artery disease patients, and other co-morbidities such as COPD, pre-existing renal disease, and thyroid disorders. The data was analyzed using SPSS software. All participants/attenders provided written informed consent, and the study was approved by the Ethical Committee of ASCOMS Jammu.

RESULTS

In the present study, we observed that out of a total of 50 patients, 6% were below the age of 30, 24% were between the ages of 30 and 40, and the remaining 70% were over the age of 40. There were 47 were male, which represents 94% of the total. Meanwhile, the remaining 3 individuals were female, accounting for only 6% of the total.

Table 1: Duration of illness and Child class

Duration in years	Child Class	Count	% within Duration in years	% within Child
<2	A	6	37.5%	75.0%
	B	7	43.8%	53.8%
	C	3	18.8%	21.4%
	Total	16	100%	45.7%
2.5-4.0	A	1	11.1%	2.5%
	B	5	55.6%	38.5%
	C	3	33.3%	21.4%
	Total	9	100%	25.7%
4.5-6.0	A	1	11.1%	12.5%
	B	1	11.1%	12.5%
	C	7	77.8%	50.0%
	Total	9	100%	25.7%
>6.0	A	0	0%	0%
	B	0	0%	0%
	C	1	100%	7.1%
	Total	1	100%	2.9%
Total	A	8	22.9%	100%
	B	13	37.1%	100%
	C	14	40.0%	100%
	Total	35	100%	100%

The table 1 presents data on the count and percentage of children in different duration categories and child classes. In the "<2" duration category, class B has the highest count of 7, accounting for 43.8% of children in this category. In the "2.5-4.0" duration category, class B again has the highest count of 5, accounting for 55.6% of children in this category. In the "4.5-6.0" duration category, class C has the highest count of 7, accounting for 77.8% of children in this category. In the ">6.0" duration category, class C has the only count of 1, accounting for 100% of children in this category. Overall, class B has the highest total count of 13, accounting for 37.1% of all children, while class A has the lowest total count of 8, accounting for 22.9% of all children.

Table 2: Duration and Mean IL6

Duration in years	No. of patients	Mean IL 6(pg/ml)
<2	16	12.281
2.6-4.0	9	14.278
4.5-6.0	9	17.067
>6.0	1	16.400
Total	35	14.143

The table 2 provides information on the mean level of IL 6 (pg/ml) in patients across different duration categories. In the "<2"

duration category, there are 16 patients with a mean IL 6 level of 12.281 pg/ml. In the "2.6-4.0" duration category, there are 9 patients with a slightly higher mean IL 6 level of 14.278 pg/ml. In the "4.5-6.0" duration category, there are also 9 patients, but with a further increase in mean IL 6 level to 17.067 pg/ml. In the ">6.0" duration category, there is only 1 patient with a mean IL 6 level of 16.400 pg/ml. Overall, across all duration categories, there are a total of 35 patients with an average mean IL 6 level of 14.143 pg/ml.

Table 3: Child class and variceal grading

Child Class	Variceal Grade	Normal	1	2	3	4	Total
A	Count	10	3	3	1	0	17
	% within Child Class	58.8%	17.6%	17.6%	5.9%	.0%	100%
	% within Variceal Grade	62.5%	100.0%	25.0%	20.0%	.0%	34.0%
B	Count	6	0	6	2	3	17
	% within Child Class	35.3%	.0%	35.3%	11.8%	17.6%	100%
	% within Variceal Grade	37.5%	.0%	50.0%	40.0%	21.4%	34.0%
C	Count	0	0	3	2	11	16
	% within Child Class	.0%	.0%	18.8%	12.5%	68.8%	100%
	% within Variceal Grade	.0%	.0%	25.0%	40.0%	78.6%	32.0%
Total	Count	16	3	12	5	14	50
	% within Child Class	32.0%	6.0%	24.0%	10.0%	28.0%	100%
	% within Variceal Grade	100%	100%	100%	100%	100%	100%

The table 3 shows the distribution of patients by Child class and variceal grade. In Child class A, there were 10 patients with normal varices, 3 with grade 2, 3 with grade 3, and 1 with grade 4. In Child class B, there were 6 patients with normal varices, 6 with grade 3, 2 with grade 4, and 3 with grade 5. In Child class C, there were no patients with normal or grade 2 varices, 3 with grade 3, 2 with grade 4, and 11 with grade 5. Overall, there were 16 patients in Child class A, 17 in B, and 16 in C, making a total of 50 patients. In terms of variceal grade, there were 3 patients with grade 1, 12 with grade 3, 5 with grade 4, and 14 with grade 5, making a total of 50 patients. The percentages within each Child class and variceal grade are also provided.

Table 4: Child score and Portal vein diameter

Child class	No of patients	Mean PVD(mm)
A	1	11.82
B	17	13.29
C	16	13.94
Total	34	13.00

The study conducted a comparison of the Child Pugh score with the Portal vein diameter, and the results showed that there is a statistically significant increase in the mean Portal vein diameter as the Child class increases. The mean Portal vein diameter was found to be 11.82mm for Child class A, 13.29mm for Child class B, and 13.94mm for Child class C. The overall mean Portal vein diameter for all patients in the study was 13.00mm. The p value for this comparison was 0.001, indicating a significant increase in the mean Portal vein diameter as the Child class increases.

Table 5: Child class and SAAG

Child class	No of patients	Mean SAAG
A	1	1.700
B	17	1.859
C	16	1.688
Total	34	1.774

In this study, the relationship between Child class and mean serum-ascites albumin gradient (SAAG) value was examined. The mean SAAG value for each Child class was calculated and compared to the overall mean SAAG value for all patients. However, the analysis did not reveal a significant correlation between Child class and SAAG value as the p value was found to be 0.449. Despite SAAG being an important factor in distinguishing patients with and without portal hypertension, in this study, it was not

found to be a reliable indicator for the required work.

Table 6: Child class and Serum albumin

Child class	No of patients	Serum Albumin(g/dl)
A	17	3.582
B	17	3.253
C	16	2.650
Total	50	3.172

The study found that as the Child class score increased from A to C, there was a decrease in mean serum albumin value. This relationship was found to be statistically significant with a p-value of 0.001.

Table 7: Prolongation of PT in sec with Mean IL6

Prolongation of PT(sec)	No of patients	Mean IL6(pg/ml)
< 2	28	11.011
2.1-4	15	14.760
4.1-6	6	19.233
> 6	1	25.300
Total	50	13.408

Here the comparison of PT prolongation with mean IL 6 was done. This correlation was statistically significant with a p value is 0.001.

Table 8: Prolongation of PT in sec with Mean IL6

Serum albumin(g/dl)	No of patients	Mean IL 6(pg/ml)
< 2.8	12	19.192
2.8-3.5	23	12.243
> 3.5	15	10.567
Total	50	13.408

The information presented describes the relationship between serum albumin levels (measured in g/dl) and the mean interleukin 6 (IL-6) levels (measured in pg/ml) in a group of 50 patients. The patients were divided into three groups based on their serum albumin levels: less than 2.8 g/dl (12 patients), between 2.8 and 3.5 g/dl (23 patients), and greater than 3.5 g/dl (15 patients).The mean IL-6 level for patients with serum albumin levels less than 2.8 g/dl was 19.192 pg/ml. For patients with serum albumin levels between 2.8 and 3.5 g/dl, the mean IL-6 level was 12.243 pg/ml. Patients with serum albumin levels greater than 3.5 g/dl had a mean IL-6 level of 10.567 pg/ml. Overall the mean IL-6 level for all 50 patients was 13.408 pg/ml. The correlation was statistically significant since the p value is 0.001

Table 9: Portal vein diameter and Mean IL6

Portal vein diameter in mm	No of patients	mean IL 6(pg/ml)
10	3	9.567
11	5	8.380
12	3	8.700
13	20	13.365
14	16	15.525
15	3	19.333
Total	50	13.408

Portal vein diameter was compared with mean IL-6, and this correlation was found to be statistically significant since the p value was 0.001.

Table 10: Child class and Hb%

Child Class	Hb(gm%)	< 6	6.1-8	8.1-10	> 10	Total
A	Count	3	4	4	6	17
	% within Child Class	17.6%	27.3%	23.5%	33.3%	100.0%
	% within HB	27.3%	23.5%	33.3%	28.6%	34.0%
B	Count	3	5	5	4	17
	% within Child Class	17.6%	29.4%	41.7%	35.7%	100.0%
	% within HB	27.3%	29.4%	35.7%	30.8%	34.0%
C	Count	5	3	5	3	16
	% within Child Class	31.3%	45.5%	25.0%	35.7%	100.0%
	% within HB	18.8%	25.0%	31.3%	23.1%	32.0%
Total	Count	11	12	14	13	50
	% within Child Class	22.0%	24.0%	28.0%	26.0%	100.0%
	% within HB	22.0%	24.0%	28.0%	26.0%	100.0%

The given table provides information on the distribution of hemoglobin (Hb) levels (measured in gm%) among patients in different Child Classes (A, B, and C). The patients are further divided based on their Hb levels into four categories: less than 6, 6.1-8, 8.1-10, and greater than 10. For Child Class A, out of 17 patients, 3 patients had Hb levels less than 6 gm%, 4 had Hb levels between 6.1-8 gm%, 4 had Hb levels between 8.1-10

gm%, and 6 had Hb levels greater than 10 gm%. The percentage of patients within the Child Class is also provided along with the percentage of patients within each Hb category. Similar information is provided for Child Class B and C. The last row of the table provides the total count and percentage of patients in each Hb category across all Child Classes. The correlation was not statistically significant since the p value was 0.876.

DISCUSSION

In the study conducted by Jolanta-Zuwala-Jagiello et al., it was observed that increasing values of serum IL 6 levels in patients with cirrhosis of various causes were correlated with the Child Pugh score in assessing the severity of the disease.[6] The mean values of serum IL 6 levels in patients with cirrhosis for Child class A, B, and C were 8.876, 13.041, and 18.612, respectively, which is consistent with the reference study as the p-value for statistical significance was 0.001.[6] Serum IL 6 can be used as a marker while assessing the severity of the disease in patients with liver cirrhosis in place of the modified Child Pugh score with acceptable statistical significance. However, it was not possible to determine the independence of rising serum IL 6 levels with etiological factors in this study since most of the patients included were alcoholics with all other possible causes excluded. The prevalence of alcohol use is higher among males in our country; thus, sex relationship with rising levels of IL 6 level in our study could not be done. We studied 45 alcoholics from a population of 50, excluding 2 with hepatitis C and 3 with hepatitis B-related cirrhosis. According to Vedat Goral et al., serum IL-6 levels are independent of the causes of liver disease when assessing disease severity.[7] However, in our study, we mostly included alcoholic patients after ruling out other possible causes. Of the total participants, 47 (94%) were male and 3 (6%) were female. Since alcohol use is more prevalent among males in our country, we were unable to establish a relationship between sex and rising levels of IL-6 in our study. We found that not only the Child-Pugh score but also other parameters such as mean total protein, serum albumin, portal vein diameter, and variceal grading on OGD scopy were significantly correlated with serum interleukin 6 levels. Regarding the correlation between Child Pugh score and mean total protein, we found that the mean total protein values for Child class A, B, and C were 6.41, 6.13, and 5.71 respectively. This correlation was found to be statistically significant with a p-value of 0.006. Therefore, we can use total protein values as a viable parameter to assess disease severity instead of the modified Child Pugh score, especially when calculating the score is challenging. In addition, when assessing disease severity in liver cirrhosis based on serum albumin values alone, we found that there is significant statistical significance. Specifically, the serum albumin values for Child Pugh class A, B, and C were 3.582, 3.253, and 2.650 respectively, and the p-value was approximately 0.001. Compared to total serum protein, serum albumin had greater statistical significance. If the diameter of the portal vein measured through a Portal Doppler Study is equal to or greater than 13 mm, it can be assumed that the patient has portal hypertension. In our study, we found that the mean portal vein diameter values for Child pugh class A, B, and C were 11.82 mm, 13.29 mm, and 13.94 mm, respectively. The overall mean portal vein diameter value for all 50 patients was 13 mm. The portal vein diameter was statistically correlated with the Child pugh class, with a p value of 0.001. Patients with Child pugh class B and C were found to definitely have portal hypertension as their mean values were 13.29 mm and 13.94 mm, respectively, compared to those with Child pugh class A. The grading of varices observed through OGD scopy was significantly correlated with the modified

Child pugh scoring system, with a p value of 0.001. In our study, out of the 17 patients in Child class A, 10 patients had normal OGD scopy, while 3 patients each had variceal grading of 1 and 2. None of the patients in Child class C had a normal OGD scopy, with 11 patients having grade 4 and 2 patients having grade 3 varices. Therefore, an increase in the variceal grading was observed with an increase in the Child class. The severity of varices in patients with liver cirrhosis is strongly associated with the level of serum IL 6, with a statistically significant p-value of 0.001. Higher levels of serum IL 6 were observed with higher variceal grading scores. This suggests that serum IL 6 can be used as a non-invasive way to identify varices in patients with liver cirrhosis, particularly when OGD scopy is not available or if the patient is too sick to be moved to the OGD room. Several other studies have also observed increased levels of IL-6 in patients with hepatic encephalopathy. For instance, Luo and colleagues found that IL-6 plays a role in the development of hepatic encephalopathy by contributing to hyperammonia, a common feature of liver failure.[8] Elevated ammonia levels can impair the clearance of IL-6 from the bloodstream, allowing it to cross the blood-brain barrier and cause astrocyte edema, ultimately leading to hepatic encephalopathy.[9] The activation of hepatic stellate cells (HSCs) and subsequent liver fibrosis and cirrhosis are promoted by the upregulation of IL-6 and its downstream STAT3 signaling pathway.[10] Studies have shown that IL-6 can induce excessive inflammation and oxidative stress, leading to tissue damage and further progression of liver disease.[11] This process creates a vicious cycle in which activated HSCs contribute to the progression of liver fibrosis, a phenomenon known as the inflammation-fibrosis axis.[12] As a result, IL-6 levels have been found to be associated with the severity of liver cirrhosis.[13]

Our study also found a positive correlation between portal vein diameter and serum IL 6 in patients with liver cirrhosis, with a p-value of 0.001. A higher portal vein diameter is indicative of portal hypertension, which was observed in patients with serum IL 6 levels above 13 pg/ml. Therefore, serum IL 6 levels greater than 13 pg/ml may be a useful marker for identifying portal hypertension in patients with liver cirrhosis, especially those with an alcoholic etiology. While portal Doppler study is still an important diagnostic tool in patients with liver cirrhosis, serum IL 6 can be used as a non-invasive marker for identifying portal hypertension. In addition, our study found a statistically significant correlation between serum IL 6 and serum albumin, suggesting that liver function worsens with increasing levels of serum IL 6. There was a significant statistical correlation (p-value of 0.001) between an increase in serum IL 6 level and the prolongation of Prothrombin time in patients with liver cirrhosis. The mean serum IL6 values for patients with varying degrees of Prothrombin time prolongation (< 2, 2.1-4, 4.1-6, and > 6) are 11.011, 14.760, 19.233, and 25.300 pg/ml, respectively. Therefore, knowledge of the elevated serum IL 6 value can help predict the risk of bleeding in patients with liver cirrhosis.

CONCLUSION

The present study demonstrated that serum IL-6 levels is a viable marker for assessing the severity of liver cirrhosis, and could replace the modified Child Pugh score. However, the study did not establish the independence of rising serum IL-6 levels with etiological factors, as most of the patients included were alcoholics. Additionally, the study found that several other parameters such as mean total protein, serum albumin, portal vein diameter, and variceal grading on OGD scopy were significantly correlated with serum interleukin 6 levels. The severity of

varices in patients with liver cirrhosis was found to be strongly associated with the level of serum IL-6, suggesting that serum IL-6 can be used as a non-invasive way to identify varices in patients with liver cirrhosis, particularly when OGD scopy is not available or if the patient is too sick to be moved to the OGD room. Elevated levels of IL-6 have also been associated with hepatic encephalopathy, liver fibrosis, and cirrhosis.

Declaration by Authors

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