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Vitamin D3 and Thymosin β 4 Level as a Biomarker of Prognosis in Acute on Chronic Liver Failure

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ABSTRACT
Background: Thymosin β4 could be beneficial for the treatment of chronic liver disease as it up regulates the expression of hepatocyte growth factor and induces apoptosis of hepatic stellate cells and hepatocyte regeneration. A significant correlation also exists between polymorphisms in the vitamin D receptor gene and occurrence of hepatocellular carcinoma in patients with liver cirrhosis.**Aims:** To assess vitamin D3 and thymosin β 4 level as a biomarker of prognosis in acute on chronic liver failure. **Methods:**Aprospectiveobservational study was conducted, which included a total of 50 cases of acute on chronic liver failure admitted in LokNayak Hospital, New Delhi, during October 2014 to March 2016.**Results:**Thymosin β4 and Vitamin D3 level was found to be significantly higher in survivors as compared to expired group (p value< 0.05)**.** The Kaplan-Meier analysis of survival showed a significant difference in cumulative survival of patients with an initial thymosinβ4 concentration ≤ 251.63 and > 251.63 ng/ml and vitamin D3 concentration ≤ 27.5 and > 27.5 ng/ml respectively. As a results of the Kaplan-Meier method and life table analysis, the mean survival time for patients had thymosin β4 levels > 251.63 ng/ml and vitamin D3 > 27.5 was significantly higher as compared to thymosinβ4 levels ≤ 251.63 ng/ml and vitamin D3 ≤27.5 (p-value<0.05).**Conclusions: As** thymosinβ4 and vitamin D3 are reliable indicatorsforprognosis and can be used to identify ACLF patients with poor prognosis and consider them for liver transplant.

Keywords: Acute on Chronic Liver failure, Thymosin β4, Chronic liver disease, Vitamin D3

I. INTRODUCTION:

Acute-on-chronic liver failure (ACLF) is an increasingly recognised entity encompassing an acute deterioration of liver function in patients with cirrhosis, either secondary to superimposed liver injury or due to extrahepatic precipitating factors such as infection culminating in the end-organ dysfunction.Occasionally, no specific precipitating event can be found.A characteristic feature of ACLF is its rapid progression, the requirement for multiple organ supports and a high incidence of short and medium term mortality of 50–90%.[1]There are many prognostic markers/models are available to predict the outcome of patients with ACLF in various studies.[2-4]Thymosin β4 has been shown to involved in a variety of physiologic and pathologic processes. It was also considered to play an important role in healing hypoxic injury.[5]Thymosin β4 upregulates the expression of HGF and downregulates the expression of PDGF-β receptor in human hepatic stellate cells.[6] HGF could induce apoptosis of hepatic stellate cells and hepatocyte regeneration.[7,8] So it is conceived that thymosin β4 protects the liver from injury. Vitamin D deficiency is associated with several adverse health outcomes. Vitamin D has an emerging role in regulating inflammation as well as an important role in immunomodulation. Vitamin D is linked not only to liver fibrosis but also to liver cirrhosis. A significant correlation exists between polymorphisms in the vitamin D receptor gene and the occurrence of hepatocellular carcinoma in patients with liver cirrhosis.[9,10]

In light of few studies with regard to Thymosin β4 and Vitamin D3 level as a prognostic marker in ACLF patients & no Indian studies are available till date on these markers in ACLF patients, the present study was conductedwith objective to assess the levels of these markers & its role in ascertaining the prognosis of patients with Acute on chronic Liver failure.

II. METHODS:

The present study was a prospective observational study and included a total of 50 cases of acute on chronic liver failure admitted in LokNayakHospital(LNH) during the period from October 2014 to October 2015.**Inclusion criteria**: The inclusion criteria of ACLF as per the APASL[21]guidelines. Patients with acute hepatic insult manifesting as jaundice with bilirubin≥5 mg/dL, coagulopathy with international normalized ratio [INR] ≥1.5 and complicated by clinical ascites

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and/or encephalopathy within 4 weeks of jaundice in previously diagnosed or undiagnosed chronic liver disease or cirrhosis.

Exclusion criteria: The patients of age ≤18 or ≥75 year, HCC/Extra hepatic malignancy, pregnancy, patient being taken up for transplant and who refused to participate the study, were excluded from the study.

Study protocol and overview of study procedures

All the patients were subjected to a detailed history and complete physical examination. Further evaluation was done in the form of hematological and biochemical profile, liver function tests, prothrombin time, serological studies and the serum levels of Thymosin β4 was measured using commercially available ELISA kits as described by the manufacturer's instructions and serum level of Vitamin D3 was measured by electro-chemiluminescence based immuno assay method.

Followup - Treatment was done as per treating physician. Physical examination was done daily, after 1 week and at 4 weeks, at 2 month, at 4month and at 6 month.Serum thymosin β4 level and vitamin D3 level was done as base line and correlated with course of illness. The end point of study was either recovery of illness or death. The present study was conducted to find out whether base line values of these biochemical parameters could finally correlate with outcome of disease and course of illness.

III. STATISTICAL ANALYSIS

The data was entered in MS-Excel and analyzed using SPSS software version 17. Qualitative data was expressed in percentages with 95% confidence interval. Quantitative data was expressed in mean + Standard Deviation (SD). Chi square test/Fisher's Exact test was used for qualitative variables. Independent t-test was used for quantitative variables. Cross tabulation was done to assess the relationship between dependent and independent variables. P value less than 0.05 was considered significant. Receiver Operating Characteristic (ROC) curve analysis was used to determine the optimal cut off value of various parameters.

IV. RESULTS:

The study was conducted under medicine department of LokNayak Hospital in Delhi. Total 55 patients of ACLF were included in the study. Out of them 5 patients could not followed up, because of they left hospital against medical advice. During 6 months of follow up, 30 (60.0%) patients were died and 20 (40.0%) were alive.The mean age of subjects was 51.7±11.54 years. Majority of the subjects were in the age group 41-60 years (60%) and majority of patient were male (74%).

Hematological and Bio-chemical profile of patients of ACLF:

The median (range) Haemoglobin, total leucocyte count, platelet count, blood urea, creatinine, and sodium were 9 (6.7-14.4) gm/dl , 10000 (6400-29000) cu.mm, 80000 (20000-190000) cu.mm, 62 (30-168) mg/dl, 1.4 (0.6-4.2) mg/dl, 133(120-145) mEq/dl, respectively.

The median (range) serum total bilirubin, INR, serum albumin, aspartate aminotransferase, and alanine aminotransferase were 8.9 (5.9–30) mg/dl, 2.3 (1.8–3.2), 2.4 (2.1–2.9) g %, 135.0 (69–885) U/L, and 79 (22–900) U/L, respectively. (Table 1)

Table.1: Hematological and Bio-chemical profile of patients of Acute on chronic liver failure

Parameters	Median	Range
Hb (gm/dl)	9.0	6.7-14.4
TLC (cells/cu.mm)	10000	6400-29000
Platelets (L/cu.mm)	80000	20000-190000
Urea (mg/dl)	62	30-168
Creatinine (mg/dl)	1.4	0.6-4.2
Sodium (meq/L)	133	120-145
Total protein (gm/dl)	5.90	4.5-7.1
Total Albumin (gm/dl)	2.40	2.1-2.9
INR	2.30	1.8-3.2
Total Bilirubin (mg/dl)	8.9	5.9-30.0
AST (IU/L)	135	69-885
ALT (IU/L)	79	22-900
ALP (IU/L)	109	67-175

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Acute and chronic insults:

Hepatitis E virus super-infection was the most common acute insult (30%), followed by Alcohol (20%) and sepsis (14%). The hepatotoxic drugs were responsible for acute insult in two patients and in four of them cause of acute insult could not be find out.One patient had fever, marked thrombocytopenia (20,000/mm3), and reactive dengue serology (IgG and IgM). The etiologies of CLD in most of the patients were due to alcohol (58.0%), followed by HBV cirrhosis (22.0%). In 8 % of patient etiology of CLD found to be unknown. In 15 (30%) patients the acute and chronic insult had same etiology.

Sepsis in ACLF:

In 30 (60 %) out of 50 cases of ACLF bacterial infection/sepsis was associated either as acute insult or as complication. The bacterial infections identified at the time of admission in 24 (80%) out of 30 patients were considered as acute insult. Out of 24 patients, bacterial infection/sepsis was the sole identified acute agent in 7(29.16%) patients. However, in the remaining 17(70.83%) patients, another known precipitant of ACLF was also present (five patients had HEV infection, three had HBV infection, seven had recent exposure to alcohol, one had Wilson's, and one had recent exposure to hepatotoxic drug). Six (20 %) out of thirty patients develop bacterial infections/sepsis during hospitalization as a complication of ACLF. (Figure 1)

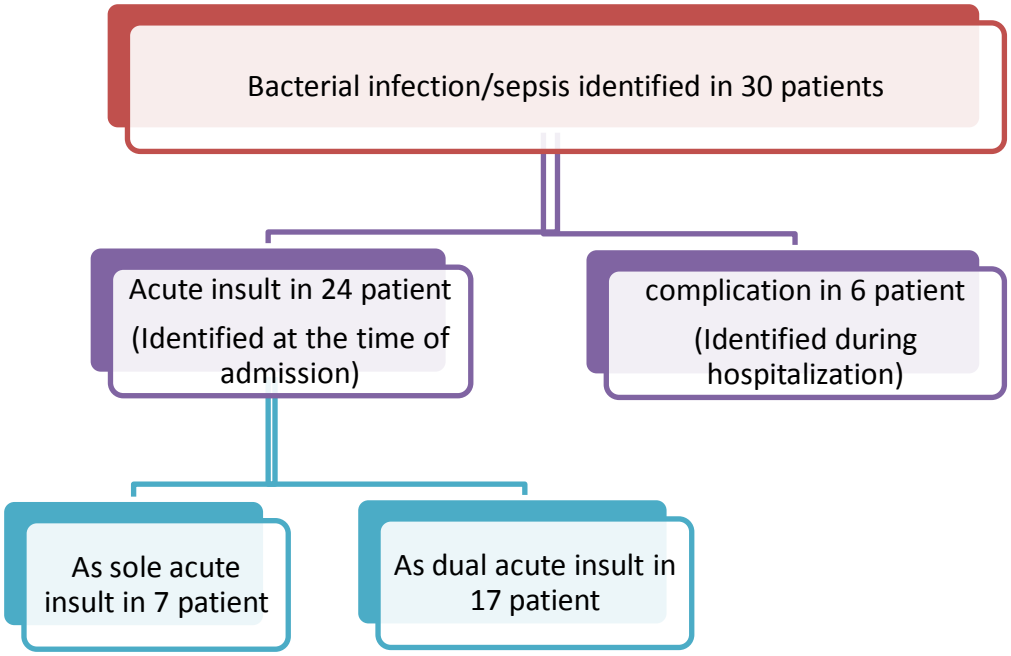

Figure.1: Sepsis in patients with ACLF

Prognostic markers of ACLF:

Various prognostic indicators such as Thymosin β4(ng/ml), Vitamin D3, MELD score, CTP score, Serum creatinine(mg/dl)and INR were found significantly different in Survived and the expired group of patients. (p value< 0.05).

After univariate analysis, multivariate logistic regression analysis was done for selected significant variables. As a result of that INR were found to be significant independent mortality predictor of poor outcome in ACLF patients [p=0.03, Adjusted Odds 28.5 CI (1.375-591.210)].

Higher grades of encephalopathy were more common in patients that expired (73.33%) compared to the patients that survived (40%) and this difference was statistically significant as calculated by chi-square test.

Thymosin β4 level was found negatively correlated with MELD score (correlation coefficient, -0.505, p-value 0.000) and CTP score (correlation coefficient, -0.518, p-value 0.000) which was found statistically highly significant.Vitamin D3 level was found negatively correlated with MELD score (correlation coefficient, -0.450, p-value 0.001) and CPC score (correlation coefficient, -0.510, p-value 0.000) which was found statistically highly significant. (Table 2)

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Table.2: Comparison of Prognostic indicators in expired v/s survived group

Prognostic indicators	Outcome	N	Mean	S.D.	p value
Thymosin β4 (ng/ml)	Survived	20	286.68	161.51	0.008
	Expired	30	170.97	132.25	
MELD score	Survived	20	27.55	2.50	0.001
	Expired	30	31.77	5.04	
CTP score	Survived	20	12.60	1.04	0.021
	Expired	30	13.43	1.30	
Serum creatinine (mg/dl)	Survived	20	1.29	0.40	0.003
	Expired	30	1.79	0.73	
INR	Survived	20	2.18	0.25	0.001
	Expired	30	2.51	0.41	

ROC curve analysis

A receiver operating characteristic curve analysis was used to determine the optimal cut off values and to test the discrimination ability of the CTP score, the MELD score, Vitamin D3 and the serum thymosin β4 concentration of patients with ACLF (Figure 2 and 3).

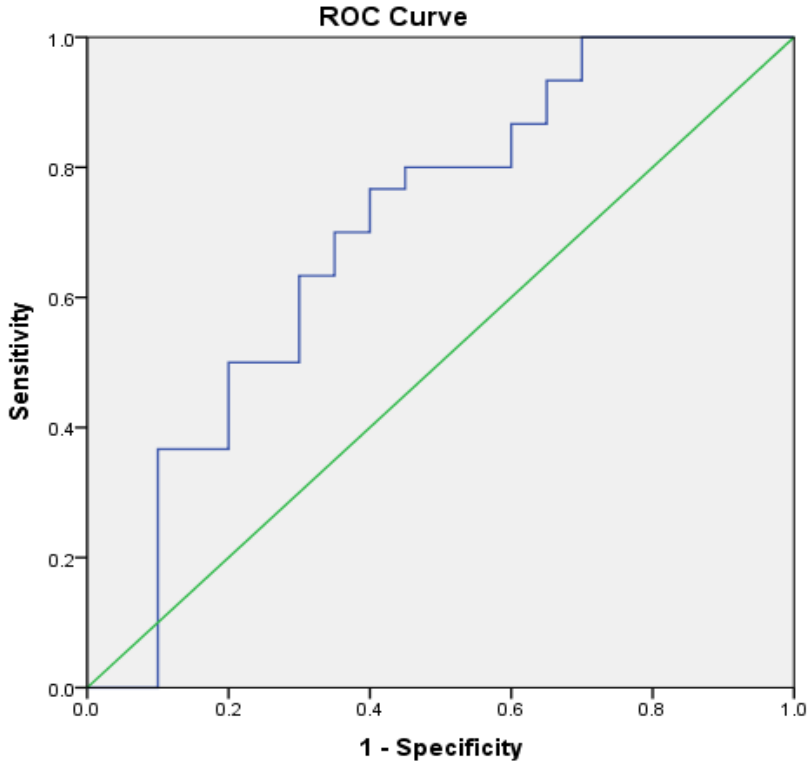

Figure.2: ROC curve for Thymosin β4

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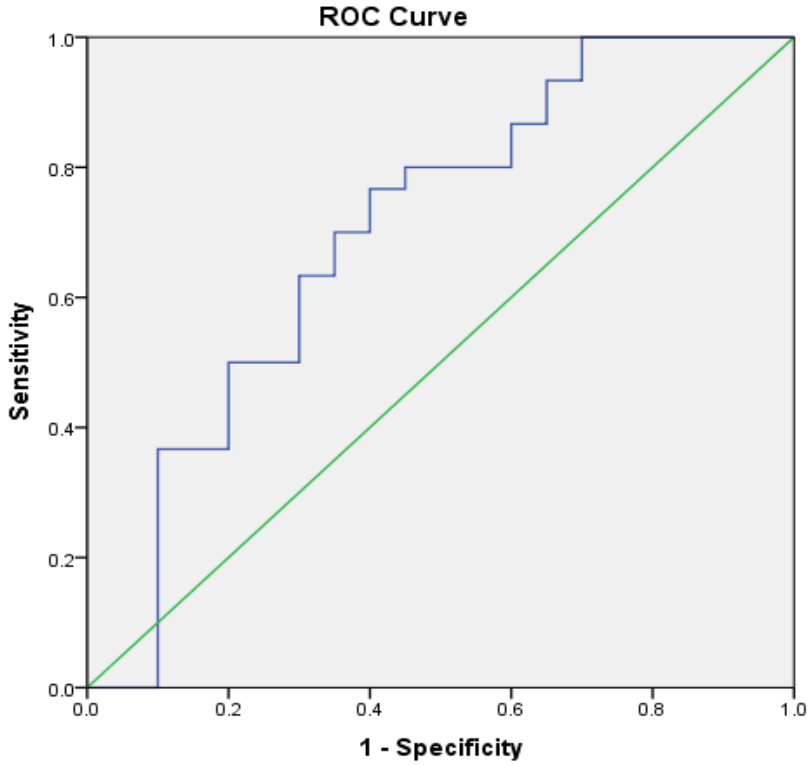

Figure.3: ROC curve for Vitamin D3

MELD score has the highest specificity and highest area under ROC (0.778) as single predictor of mortality.Thymosin β4 is a better marker than Vitamin D3 and CTP score in terms of specificity, positive predictive value, negative predictive value and AUROC (0.702).(Table 3)

Table.3. Comparison of Thymosin β4, Vitamin D3, CTP score, MELD score as individual predictor of mortality in ACLF patients

	Thymosin β4	Vitamin D3	CTP score	MELD score
Sensitivity	70.0%	73.3%	76.7%	73.3%
Specificity	65.0%	60.0%	55.0%	70.0%
Positive predictive value	79.3%	75.0%	71.9%	78.6%
Negative predictive value	66.6%	59.0%	61.1%	63.6%
AUROC	0.702	0.697	0.693	0.778

Analysis of survival time of ACLF patients

The Kaplan-Meier analysis of survival showed a significant difference in cumulative survival of patients with an initial CTP score ≤ 12.5 and > 12.5, a MELD score ≤ 28.5 and > 28.5 and a Thymosinβ4 concentration ≤ 251.63 and > 251.63 ng/mL, Vitamin D3 concentration ≤ 27.5 and > 27.5 ng/mL respectively. (Figure 4)

As a results of the Kaplan-Meier method and life table analysis, the mean survival time for patients had Tβ4 levels > 251.63 ng/mL, Vitamin D3 > 27.5 and MELD score ≤ 28.5 was significantly higher as compared to Tβ4 levels ≤ 251.63 ng/mL, Vitamin D3 ≤27.5 and MELD score >28.5 (p-value<0.05, log rank analysis of survival). (Table 4)

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Table.4: The Kaplan-Meier and life table analysis for the patients with ACLF

Predictors of mortality		Mean survived time (Mean±SE, 95% CI, days)	p-value (log rank analysis)
Thymosin β4 (ng/ml)	≤251.63	8.048±1.445 (5.215-10.880)	0.012
	>251.63	15.889±3.780 (8.480-23.298)	
Vitamin D3 (ng/ml)	≤27.5	6.955±0.920 (5.152-8.758)	0.001
	>27.5	19.875±4.060(11.918-27.832)	
MELD score	>28.5	16.750±4.148 (8.620-24880)	0.014
	≤28.5	8.091±1.388 (5.371-10811)	
CTP score	>12.5	13.571±4.180 (5.379-21.764)	0.207
	≤12.5	9.435±1.703 (6.097-12.773)	

V. DISCUSSION:

ACLF is a disease with stormy progression and poor outcome. Acute super infection with a hepatitis virus is a well-recognized cause of ACLF. In the present study hepatitis viruses were most common acute insult identified at the time of admission and hepatitis E virus was found to be commonest [15(30%)] amongst them followed by HBV and HAV in 5 (10%), and 5 (10%) of patients, respectively. Similarly findings were reported by other Indian studies.[11-13]However various studies in western countries reported the commonest insults was alcoholic hepatitis followed by sepsis and upper gastrointestinal bleed.[2,14]This could be because of different study settings and population.

Sepsis is defined as the presence of SIRS in the presence of infection with or without the presence of multi-organ dysfunction. SIRS is an important pathophysiological mechanism of ACLF and multi-organ dysfunction. Patients with underlying CLD may have deranged parameters of SIRS even in the absence of sepsis/infection. Establishing infection/sepsis as insult initiating the acute injury in compensated CLD should be considered only in the presence of definite evidence of infection and SIRS and when all known common hepatic acute events, such as acute viral hepatitis, viral or autoimmune hepatitis flare, and exposure to drugs and toxins, are excluded by appropriate history and investigations.

CANONIC Study is in favour of including bacterial infection/sepsis as acute insult.[15]More recently, some authors have started including SBP/SBE as an acute insult. We have also included SBP/SBE as acute insult. We found that 30 out of 50 patients with ACLF had evidence of bacterial infection (Figure 1). Out of 30 patients, bacterial infection was identified at the time of admission in 24 patients and considered as acute insult. In our study, six cases (20 %) of bacterial infections (out of 30 patients of documented infection) were identified during hospitalization (with available baseline parameters) and were considered as complication. In a European study, infection during hospitalization was noted in 58 % of the patients of ACLF which was much higher compared to our study.[16]However, comparison of these studies is difficult because of following reasons: etiological spectrum was significantly different, as the 87 % of ACLF patients in the European study had alcoholic liver disease. Moreover, the study population was different.Role of variceal bleeding as acute insult is possibly the most controversial of all. In APASL(2009) consensus, most experts argue against the inclusion of variceal bleed in the list of acute insult.[17]We did not include variceal bleed as an acute insult.

Univariate analysis showed high INR, and high serum creatinine,to be significantly associated with the mortality. On multivariate analysis only high INR was found to be independent baseline predictors of mortality inACLF survivors & non-survivors ($p < 0.03$). A study done by Garg et alconcluded similar results.[2]Higher grades of encephalopathy were more common in patients who expired (73.3%) as compared to the patients who survived (40%) and this difference was statistically found to be significant. Hepatic encephalopathy, low serum sodium, and high INR were found to be independent baseline predictors of mortality in a study from China.[18]

THYMOSIN β4 LEVEL

Thymosin β4 levels have been previously investigated as prognostic predictor in ACLF patients.[38]In our study, mean serum Thymosin β4 levels at admission was found to be significantly lower in ACLF patients who expired (170.97±132.25ng/ml) as compared to the patients who survived (286.68±161.51ng/ml). This was comparable to the findings of Luiet al.[19]

Receiver operating characteristic curve analysis for Thymosin β4 for predicting mortality revealed an area under curve of 0.702, indicating that it is a good predictor of mortality.

The Kaplan-Meier analysis of survival showed a significant difference in cumulative survival of patients with an initial Tβ4 concentration ≤ 251.63 ng/ml and > 251.63 ng/ml. Serum Thymosin β4 levels ≤ 251.63 ng/ml at admission suggestive of poor prognosis in ACLF patients and indicating that they were the candidates for liver transplantation, which could be life saving for these patients.The findings of the present study were found to be similar to a study reported by Liu et al[19]who showed that low levels of Thymosin β4 in ACLF non-survivors compared to survivors & concluded that this molecule could be used as a marker for prognosis in patient with ACLF.

VITAMIN D3

In our study, mean serum Vitamin D3 levels at admission was found to be significantly lower in patients who expired (21.15±10.34 ng/ml) as compared to the patients who survived (28.35±8.45 ng/ml).

Receiver operating characteristic curve analysis for Vitamin D3 for predicting the mortality revealed that an area under curve was 0.697, indicating that it was a good predictor of mortality.

The Kaplan-Meier analysis of survival showed a significant difference in cumulative survival of patients with an initial Vitamin D3 concentration ≤ 27.5 and > 27.5 ng/mL.Serum Vitamin D3 levels ≤ 27.5 ng/ml at admission suggestive of poor prognosis in ACLF patients. Studies on Vitamin D3 as a prognostic marker in acute on chronic liver failure could not be located even with the best of my effort. However some studies reported role of vitamin D3 in chronic liver disease of various etiologies such as a study done by Canan et alreported that the patients with chronic hepatitis B virus infection had a lower 25-OHD level compared with naturally immunized and the control group.[20] Another study by Petta et al demonstrated that the low serum 25-OHD levels was associated with low sustained viral response to interferon treatment in patients chronically infected with genotype 1 hepatitis C virus.[21]

VI. CONCLUSION

On comparing the various prognostic markers it can be concluded that MELD score has the best specificity and AUROC. Although the study result does not show that Tβ4 and vitamin D3 were superior to MELD score, Tβ4 level and Vitamin D3 are still a novel and reliable indicator of the prognosis of patients with ACLF. These markers can be used to identify ACLF patients with poor prognosis & consider them for liver transplant. Further studies with these novel markers would be valuable to assess the prognosis of ACLF patients & better prioritize patients for liver transplantation.

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