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Research Article

Plasma Follistatin/Serum Activin A Ratio in Predicting the Outcome of Acute Liver Failure in Children

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Abstract

Background/objectives: Follistatin (FST) and Activin A have been described as major regulators of liver pathology and hepatocyte regeneration. FST bind with high affinity to Activin A and this complex formation block the Activin signaling. The aim of the study was to evaluate the value of plasma FST/Serum Activin A (F/A) ratio in predicting the outcome of Acute Liver Failure (ALF) in children.

Methods: This prospective study included 76 children divided into three groups; ALF, Acute Hepatitis (AH) as diseased controls and Healthy Controls (HC) group. Complete clinical and laboratory assessment were done for all patients. Plasma FST and Activin A serum levels for all study groups.

Results: Serum Activin A level of ALF group was significantly higher than that of AH and HC groups, and F/A ratio of ALF group was significantly lower than that of other groups. Serum Activin A level at a cutoff value of 856 pg/ml can differentiate between ALF survivors group (less lower) and ALF non-survivors (equal or more higher) with high 83.3% specificity. F/A ratio at a cutoff value of 8.085 can differentiate between ALF survivors group (higher) and ALF non-survivors (equal or less lower) with high 83.3% sensitivity.

Conclusion: Comparison of clinical performance of each of Serum Activin A level, F/A ratio, International Normalization Ratio (INR), serum albumin level and Pediatric End-Stage Liver Disease (PELD)/ Model for End-Stage Liver Disease (MELD) scores in predicting ALF prognosis in children revealed that Serum Activin A level and F/A ratio are the most reliable tests.

Keywords: Follistatin; Serum Activin A; Acute Liver Failure; Children; Encephalopathy

Introduction

The Pediatric Acute Liver Failure (ALF) Study Group has defined ALF in the case of having no known evidence of chronic liver disease, biochemical evidence of Acute Liver Injury (ALI), and hepatic-based coagulopathy defined as prothrombin time (PT) ≥ 15 seconds or International Normalized Ratio (INR) ≥ 1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy, or PT ≥ 20 seconds or INR ≥ 2.0 regardless of the presence or absence of clinical hepatic encephalopathy [1].

Liver Transplantation (LT) considered being the only treatment for patients with irreversible liver injury [2]. Many of prognostic models have been evaluated to predict ALF patient's outcome to select those in need for LT. The most widely applied ones are the King's College Criteria (KCC), Clichy's criteria, and the Model for End-Stage Liver Disease (MELD) [3].

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Activins are members of the transforming growth factor β (TGF-β) super family, which exert their functions through heterodimer receptor complexes consisting of type I and type II receptors that differ from the TGF-β receptors. Activin A is the most abundant Activins-variant. Activin A has a pro-apoptotic factor for hepatocytes and act as a negative regulator of hepatocyte proliferation in the regenerating liver with a possible role of cessation of the regeneration process [4].

Follistatin (FST) acts as antagonist of Activin activity. FST, which is expressed in most organs expressing Activins, binds mature secreted Activin A with high affinity. Complex formation with FST completely inhibiting receptor binding of Activin A, thus blocking Activin signaling [5].

The aim of the current study was to evaluate the role of plasma FST/serum Activin A (F/A) ratio in predicting the outcome of ALF in children in comparison with the other predictive scores (MELD score, Pediatric End-Stage Liver Disease (PELD) score and KCC).

Materials and Methods

Study population

This prospective study included 76 children recruited over a period of two years (August 2017 to August 2019), from inpatient ward and outpatient clinic of the Pediatric Hepatology, Gastroenterology, and Nutrition department, National Liver Institute, Menoufia University. These children were divided into three groups; Group1: ALF group (n=30) all of whom full filled the criteria of Pediatric ALF Study Group definition of ALF, Group 2: acute hepatitis (AH) (n=24) as diseased controls and Group 3: healthy controls (HC) (n=22). Those who received any treatments that may have affected circulating FST

and Activin A levels, such as glucocorticoidsor antithrombin III were excluded. Informed written consent was obtained from the parents or the legal guardians of all children. The study was approved by the Research Ethics Committee of National Liver Institute, Menoufia University.

Investigations of the 1st group (ALF group) (n=30)

Complete laboratory analyses at admission were according to European Association for the Study of the Liver (EASL) [6]. MELD and PELD scores were calculated on the day of admission for all children with ALF according to Wiesner et al. [7].

Investigations of the 2nd group (AH group) (n=24)

Complete liver function tests, Complete Blood Count (CBC), viral markers for viral causes (Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), and if negative: Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), Herps simplex, C-reactive Protein (CRP), culture for bacterial causes, auto antibodies and total Immunoglobulin G (IgG) were done).

Investigations of the 3rd group (HC group) (n=22)

Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), CBC were done.

Follistatin plasma level

For all groups, on the day of admission, it was done by ELISA technique, by kit from R&D system, Minneapolis, MN, USA. Cat. No. DFN00 (minimum detection limit is 29 pg/ml).

Activin A serum level

For all groups, on the day of admission, it was done by ELISA technique, by kit from R&D system, Minneapolis, MN, USA. Cat. No. DAC00B (minimum detection limit is 3.67 pg/ml).

If a patient has had 2 or more hemodialysis treatments in the week prior to the time of the scoring, Creatinine will be set to 4 mg/dL, the maximum creatinine level allowed in the model. Laboratory values less than 1.0 are set to 1.0 for the purposes of MELD score calculation. For patients with urea cycle disorders, organic acidemia or hepatoblastoma, the PELD score is set at 30. Laboratory values <1.0 are set to 1.0 for the purposes of PELD score calculation. As the causes of ALF cases in this study did not include paracetamol toxicity so we used the criteria of non-paracetamol causes to determine prognosis of ALF cases on the day of admission [8].

Statistical analysis

Descriptive results were expressed as mean ± standard deviation (mean ± SD) or number and percentage. For quantitative data, significance was tested either by independent sample t-test or Mann-Whitney U-test according to the nature of the data. A paired t-test was used to assess the difference in serum cytokine levels before and after the Kasai operation. For qualitative and categorical data, significance was tested by χ^2-test or Fisher's exact test. Correlation was tested by Spearman's test. Results were considered significant if P<0.05. Statistical analysis was performed using SPSS software version 13 (SPSS Inc, Chicago, IL, USA).

Results

There was no significant statistical difference in the age and the sex between ALF and AH groups. In comparison of LFTs between the two groups; TB, DB, PT and INR were significantly higher in ALF group than in AH group, while there was no significant statistical difference between the two groups in AST, ALT, albumin or AST/ALT ratio. The ultrasonographic signs showed a significant higher frequency of splenomegaly in ALF children than in those with AH, while there was no significant difference in the frequency of hepatomegaly between the two groups (Table 1).

In comparison of ALF survivors and non-survivors there was no significant difference between the two groups in age, sex, bleeding tendency, presence of convulsions, presence of ascites, jaundice-liver failure interval, TB, DB/TB ratio, AST, ALT, blood ammonia, serum creatinine, hemoglobin, platelets or white blood cell count. Also, there was no significant difference between them in serum AFP or serum phosphorus. ALF non-survivors had significant higher INR (5.1 ± 2.5) and lower serum albumin level (3.1 gm/dl ± 0.4 gm/dl) than survivors (3.5 ± 2.3) (3.5 gm/dl ± 0.4 gm/dl) respectively.

Correlation between Activin A, FST, F/A ratio and other biochemical parameters

Serum Activin A positively correlated with each of TB, AST, ALT, PT and INR and negatively correlated with serum albumin, while F/A ratio positively correlated with serum albumin and negatively correlated with TB, PT and INR, and these correlations were all significant statistically. F/A not significantly correlated with AST or ALT, also both F/A ratio and Activin A not significantly correlated with blood ammonia. FST positively correlated with ALT, while not significantly correlated with any of the other biochemical parameters (Table 2).

Table 1: Demographic, laboratory and ultrasonographic characteristics of ALF and AH groups.

	ALF (n=30)	AH (n=24)	P-value
Age (years)	6.3 ± 4.9	7.4 ± 4.2	0.494
Male (n%)	15 50%	15 62.5%	0.654
TB (mg/dl)	24.7 ± 10.1	11.1 ± 11.3	0.0001
DB (mg/dl)	16.5 ± 7.6	6.5 ± 5.2	0.0001
ALB (gm/dl)	3.3 ± 0.5	3.5 ± 0.4	0.087
AST (IU/L)	1155.3 ± 1002.9	927.1 ± 683.3	0.326
ALT (IU/L)	1077.2 ± 997.8	964.9 ± 544.8	0.602
PT (sec)	40.9 ± 16.9	13.4 ± 1.9	0.0001
AST/ALT ratio	1.17± 0.46	1.02± 0.48	0.127
INR	4.4 ± 2.7	1.2 ± 0.2	0.0001
Splenomegaly (n%)	10 33.3%	2 8.3%	0.028
Hepatomegaly (n%)	16 53.3%	13 54.2%	0.585

TB: Total Bilirubin; DB: Direct bilirubin; ALB: Albumin; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; PT: Prothrombin Time; INR: International Normalization Ratio

Table 2: Correlation between activin A, FST, F/A ratio and other biochemical parameters.

	Serum Activin A		FST		F/A ratio	
	r	P-value	r	P-value	r	P-value
TB (mg/dl)	0.306*	0.024	-0.106-	0.445	-0.405**	0.002
ALB (gm/dl)	-0.331*	0.015	0.056	0.687	0.300*	0.028
AST (IU/L)	0.232*	0.044	0.18	0.119	-0.222	0.054
ALT (IU/L)	0.241*	0.036	0.232*	0.043	-0.126	0.279
PT (sec)	0.688**	0.001	0.182	0.189	-0.471**	0.001
INR	0.596**	0.001	0.226	0.1	-0.383**	0.004
Ammonia (umol/L)	-0.095	0.616	0.222	0.238	0.196	0.299

TB: Total Bilirubin; DB: Direct Bilirubin; ALB: Albumin; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; PT: Prothrombin Time; INR: International Normalization Ratio

*:p.value<0.05

**:p.value<0.01

Plasma FST, Serum Activin A and F/A ratio in the study groups

Plasma FST level of ALF group (4285 pg/ml ± 1787.7 pg/ml) was significantly higher than that of HC group (3186.32 pg/ml ± 1418.1 pg/ml) and was not significantly different from that of AH group (4345.8 pg/ml ± 2767.6 pg/ml), also plasma FST level of AH group was higher than that of HC group but without significant difference. Serum Activin A of ALF group (881.8 pg/ml ± 430.6 pg/ml) was significantly higher than that of AH group (407.8 pg/ml ± 248.7 pg/ml) and HC group (247.6 pg/ml ± 109.2 pg/ml), also its level in AH group was significantly higher than that of HC group. The F/A ratio of ALF group (5.87 ± 2.95) was significantly lower than that of AH group (12.9 ± 7.2) and HC group (14.5 ± 8.74), while AH group had lower F/A ratio than that of HC but this difference was not significant statistically (Figure 1).

Despite plasma FST level of ALF non-survivors (4584 pg/ml ± 2028 pg/ml) was higher than that of survivors (3837 pg/ml ± 1304 pg/ml) this was not significant statistically. Serum Activin A of ALF non-survivors (1082 pg/ml ± 405 pg/ml) was significantly higher than that of survivors (582 pg/ml ± 267 pg/ml) while F/A ratio of non-survivors (4.9 ± 2.9) was significantly lower than that of survivors (7.4 ± 2.4).

Prognostic value of Serum Activin A and F/A ratio in pediatric in ALF group

Serum Activin A level at a cutoff value of 856 pg/ml can differentiate between ALF survivors (lower) and non-survivors (higher) with 72.2% sensitivity, 83.3% specificity, 86.7% Positive Predictive Value (PPV), 66.7% Negative Predictive Value (NPV), 77% accuracy and AUROC was 86% and was significant statistically. on the other hand, F/A ratio at a cutoff value of 8.085 can differentiate between survivors (higher) and non-survivors (lower) with 83.3%

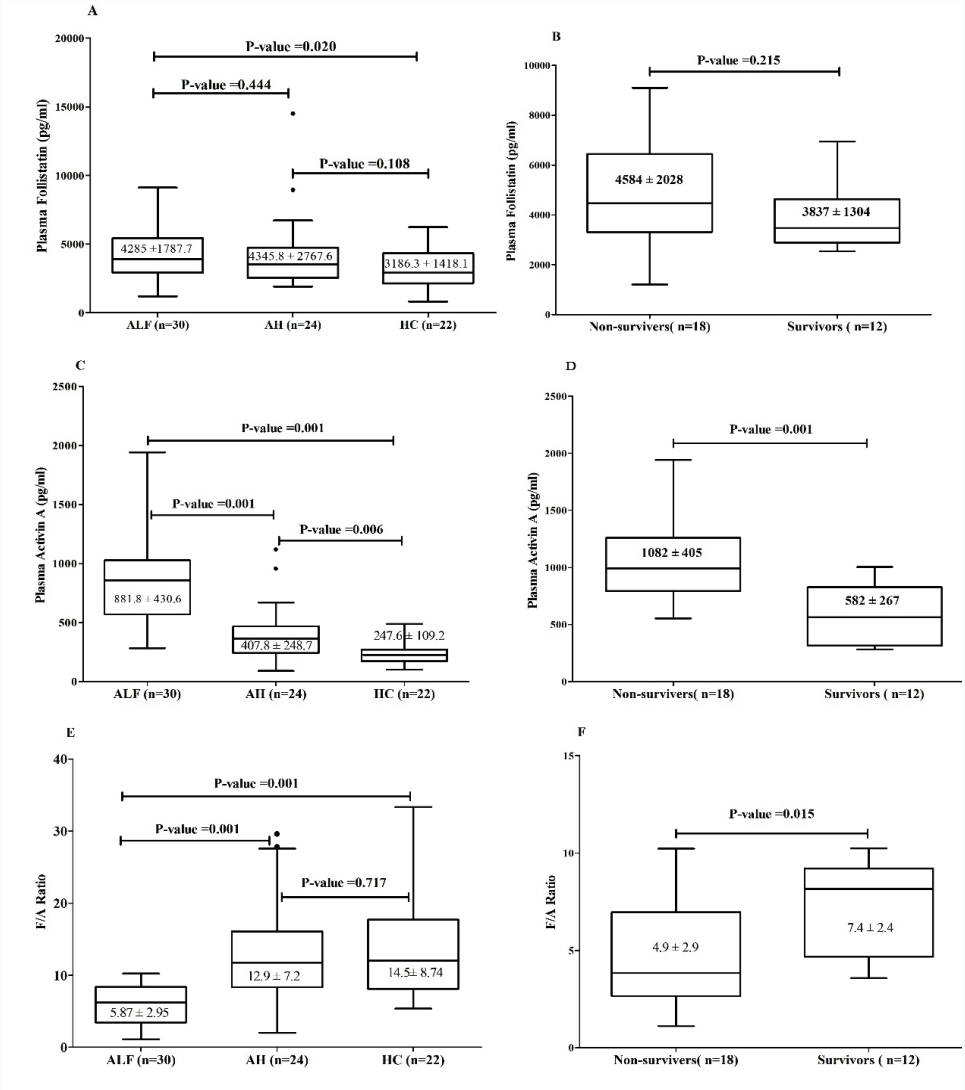


Figure 1: Comparison of plasma FST level (pg/ml), serum activin A level (pg/ml) and F/A ratio between ALF, AH and HC groups and ALF survivors and non survivors.
Comparison of A) plasma FST level (pg/ml), C) serum activin A level (pg/ml) and E) F/A ratio between ALF, AH and HC groups.
Comparison of B) plasma FST level (pg/ml), D) serum activinA level (pg/ml)and F) F/A ratio between ALF survivors and non-survivors.

sensitivity, 66.7% specificity, 78.9% PPV, 72.7% NPV 77% accuracy and AUROC was 76% which was significant statistically.

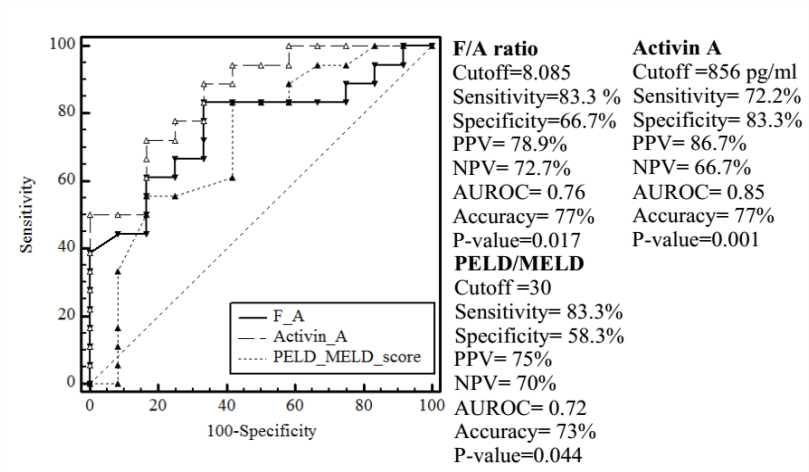
Kings College Criteria (KCC) and PELD/MELD score in ALF group

In our study 16 cases of ALF were listed for LT according to KKC, 12 (75%) of them died and 4 (25%) survived without LT. While 14 cases were not listed for LT according KKC, 6 (42.9%) of them died where 8 (57.1%) survived. There was no significant statistical difference between the two groups as regard KKC (Table 3). While PELD/MELD score in the day of admission was significantly higher in non-survivors (32.7 ± 6.5) than in survivors (26.8 ± 9.4) (Table 4).

Comparison of prognostic value of each of Serum Activin A level, F/A ratio, INR, serum albumin level and PELD/MELD score D1 in ALF group

Serum Activin A level (AUROC=86%) and F/A ratio (AUROC=76%) are the most statistically significant reliable tests, also Serum Activin A level has the highest specificity, PPV and statistical significance, while F/A ratio has the highest NPV and high sensitivity. PELD/MELD score and serum albumin level have the lowest specificity, also PELD/MELD score has the least statistically significant reliability (AUROC=72%) (Figure 2).

A:



B:

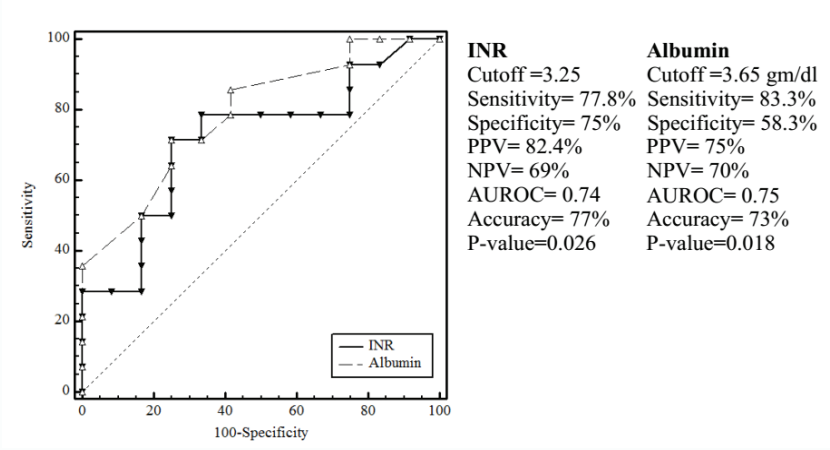


Figure 2: Performance of serum activin A level, F/A ratio, INR, serum albumin level and PELD/MELD score in discriminating between ALF survivors and non-survivors.
A: Performance of F/A ratio, serum activinA level and PELD/MELD score.
B: Performance of serum albumin level and INR
F/A:follistatin/activin ratio
INR: international normalization ratio
PELD: pediatric end-stage liver disease
MELD: model for end-stage liver disease

Table 3: Comparison between the actual prognosis of ALF cases and the predicted prognosis by Kings College criteria (KKC) D1.

KKC D1	Prognosis of ALF (n=30)						
	Survived (n=12)		Died (n=18)		Total		P-value
	n	%	n	%	N	%	
List	4	0.25	12	0.75	16	1	0.073
Do not list	8	0.571	6	0.429	14	1	

Kings College criteria (KKC); D=Day of Admission

Table 4: Comparison of PELD/MELD score D1 between ALF survivors and non-survivors.

	Survived (n=12)	Died (n=18)	P-value
	Mean ± SD		
PELD/MELD Score D1	26.8 ± 9.4	32.7 ± 6.5	0.043

PELD: Pediatric End-Stage Liver Disease; MELD: Model End-stage Liver Disease; D1: Day of Admission

Discussion

Pediatric Acute Liver Failure (PALF) is a potentially devastating condition which occurs in previously healthy children of all ages and frequently leads to a rapid clinical deterioration. An identified cause for liver injury is lacking in approximately 30% of cases. Children with undetermined diagnosis have lower spontaneous survival and higher rates of transplantation and death than other diagnostic groups [9]. Rodgarkia-Dara et al. [10] reported that increased production of Activin A was suggested to be a contributing factor to impaired hepatocyte regeneration in ALF and to overproduction of extracellular matrix in liver fibrosis [10].

Activin-A and FST are expressed by the hepatocyte and have been described as major regulators of liver biology, liver regeneration, and liver pathology [10], and have been proposed as diagnostic/prognostic markers for a variety of liver diseases. Serum levels of Activin-A and FST have been studied in several liver pathologies and alterations in their levels were correlated with diseases severity [11,12].

In our study, we found that ALF group had a significant higher Serum Activin A level and lower F/A ratio than that of each of AH and HC groups, and had significant higher mean value of plasma FST level than that of HC group, while there was no significant statistical difference as regard plasma FST level between ALF and AH groups. Serum Activin A was significantly higher in AH group than HC group, while there was no significant statistical difference in plasma FST level, or F/A ratio between the two groups. Also, our study revealed that ALF non-survivors had a statistically significant higher mean value of serum activin A and lower F/A ratio than those who survived, while there was no significant statistical difference between the two groups as regard plasma FST level.

Serum Activin A was significantly higher in AH group than HC group, while there was no significant statistical difference in plasma FST level, or F/A ratio between the two groups. Our study revealed that ALF died group had a statistically significant higher mean value of serum Activin A and lower F/A ratio than those of survived group, while there was no significant statistical difference between the two groups as regard plasma FST level.

Similarly, Lin et al. [13], reported, (1) Activin A levels in patients with ALF were significantly elevated when compared with those in patients with AH and control group, and that plasma FST level in ALF group was significantly elevated when compared with controls, (2) F/A ratio in patients with ALF was significantly decreased when compared with that in patients with AH and controls and (3) Serum Activin A level was significantly higher non survivors than in survivors and that F/A ratio was significantly lower in non survivors than in survivors. In addition Hughes and Evans [14] found both Serum Activin A and plasma FST levels were significantly increased in the patients with ALF compared to normal controls, and that F/A ratio in ALF cases was significantly lower than in normal controls.

On the other hand Lin et al. [13], reported that (1) plasma FST levels in patients with ALF were significantly elevated when compared with those in AH patients, (2) F/A ratio in patients with AH was significantly elevated when compared with that in controls, (3) no significant differences in Activin A levels between patients with AH and control group and (4) plasma FST level was higher in non survivors than in survivors. Similar results reported by Hughes and Evans [14] as they found both Serum Activin A and plasma FST levels were significantly increased in the patients with ALF compared to normal controls, and that F/A ratio in ALF cases was significantly lower than in normal controls.

We found that there was a significant positive correlation between Serum Activin A level and TB, PT, INR, AST and ALT, while there was a significant negative correlation between its level and serum albumin level. There was no significant correlation between its level and blood ammonia. F/A ratio showed a significant negative correlation with TB, PT and INR, while showed a positive correlation with serum albumin level. But there was no significant correlation between the ratio and AST, ALT or blood ammonia. There was no significant correlation between plasma FST and LFTs except a significant positive correlation with ALT.

We reported that, serum Activin A level at a cutoff value of 856 pg/ml can differentiate between ALF survivors (lower) and non-survivors (equal or higher) with 72.2% sensitivity and 83.3% specificity. While F/A ratio at a cutoff value of 8.085 can differentiate between survivors (higher) and non-survivors (equal or lower) with 83.3% sensitivity and 66.7% specificity. Also, we found that PELD/MELD score at a cutoff value of 30 can differentiate between survivors (lower) and non-survivors (equal or higher) with 83.3% sensitivity and 58.3% specificity, while there was no significant statistical difference between the two groups as regard KCC.

By comparing the clinical performance of each of Serum Activin A level, F/A ratio, INR, serum albumin level and PELD/MELD score in prediction of ALF prognosis using ROC curve we found that Serum Activin A level (AUROC=86%) and F/A ratio (AUROC=76%) are the most reliable tests, also Serum Activin A level has the highest statistically significant specificity, and PPV while F/A ratio has the highest NPV. PELD/MELD score and serum albumin level have the lowest specificity, also PELD/MELD score has the least reliability (AUROC=72%).

Based on our observation that Serum Activin A level was significantly higher in ALF group than in AH and control groups, moreover its level was significantly higher in died cases with ALF than those who survived. Ichikawa et al. [15] found that blockade of the action of Activin leads to the initiation of DNA synthesis in intact liver and that Activin suppress hepatocyte growth even in intact liver and may play a critical role in the maintenance of constant liver mass. So in the view of these findings we suppose that Activin A has a pivotal role in the pathogenesis of ALF and loss of liver mass.

Also, Serum Activin A level and F/A ratio not only can help in predicting the outcome of ALF in children but also can be a corner stone for developing a new treatment and radical solution of ALF.

Also Kogure et al. [16], found that infusion of FST into the portal vein of the rat induced DNA synthesis as the DNA content of the rat liver was significantly elevated after 72 hours and returned to the basal value within 120 hours.

Kanamoto et al. [17], reported that rats with ischemic/reperfusion hepatic injury which were treated with recombinant human FST infused into portal vein had a better outcome than those who not treated with specific therapy and they proposed that FST has therapeutic potential for the prevention and treatment of hepatic damage leading to ALF.

Conclusion

Children with ALF had significant higher Serum Activin A level and lower F/A ratio than that of both AH and HC groups. Also, plasma FST level of ALF group was significantly higher than that of HC group but was not significantly different from that of AH group. Comparison of clinical performance of each of Serum Activin A level, F/A ratio, INR, serum albumin level and PELD/MELD scores in predicting ALF prognosis in children revealed that Serum Activin A level and F/A ratio are the most reliable tests. Serum Activin A level has the highest specificity, PPV and statistical significance while F/A ratio have the highest NPV and high sensitivity. Serum Activin A and plasma FST are main players in ALF pathogenesis and is the cornerstone in determining its prognosis. Upon the previous results we found that Serum Activin A level and F/A ratio have a pivotal role in the prediction of the outcome of ALF in children and seem to have a crucial role in the severity and the pathogenesis of ALF. In future studies with larger number of cases Activin A serum level and F/A ratio can be validated as the most sensitive and specific predictors of ALF outcome in children that may open a way of hope as a therapeutic potential for the treatment of the miserable fate of patients with ALF with liver transplantation.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

Ethical approval

The study was approved by the Research Ethics Committee of National Liver Institute, Menoufia University.

Informed consent

A signed informed consent was obtained from the parents or the legal guardians of the patients before starting the study.

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