

Original Research Article

Liver function tests as a prognostic indicator in Pediatric Intensive Care Unit (PICU)

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Received: 19 February 2018

Accepted: 28 March 2018

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ABSTRACT

Background: Frank liver failure is incompatible with life. Severity of liver disease is reflected in clinical signs or biochemical alterations. Hepatic dysfunction indicates poor outcome in critically ill patients, but no large systematic investigation into its exact incidence and prognostic relevance has been performed in different population groups.

Methods: All PICU admissions during the study period were included. Pattern of admission LFT (Liver Function Tests) was reported. Relationship between clinical events and patient outcome with the LFT panel on day 1 and day 3 were reported. Association between final outcome and day 7 LFT was explored.

Results: Deranged AST (Aspartate Transaminase), ALT (Alanine Transaminase), Bilirubin, Albumin, PT (Prothrombin time) and INR (International Normalized Ratio) on Day1 and 3 had significant association with increased requirement of inotropic and ventilatory support as well with increased mortality. LFT parameters on day 7 showed significant correlation between normal AST, ALT, bilirubin, PT and INR with improved survival.

Conclusions: LFT's should be essential part of biochemical profile and doctors caring for sick patients in peripheral hospitals should consider for early referral of patients to higher centers based on LFT parameters for the advanced care they deserve.

Keywords: Critically ill children, LFT, Prognosis

INTRODUCTION

Hepatocytes perform numerous and vital roles in maintaining homeostasis and health. Frank liver failure is incompatible with life, and the functions of the liver are too complex and diverse to be sub served by a mechanical pump, dialysis membrane, or concoction of infused hormones, proteins and growth factors.¹ The severity of the liver disease may be reflected in clinical signs (the occurrence of encephalopathy, variceal hemorrhage, worsening jaundice, apparent shrinkage of liver mass owing to massive necrosis, or onset of ascites) or in biochemical alterations (hypoglycemia, hyperammonemia, electrolyte imbalance, continued hyperbilirubinemia, marked hypoalbuminemia, or a

prolonged pro thrombin time (PT) or INR that is unresponsive to parenteral administration of vitamin K).²

Critically ill patients are most carefully observed and monitored in the indoor hospital setting with many tests being performed on sequential basis. In critically ill patients with multiple organ failure liver dysfunction is often overshadowed or missed.³ Hepatic injury in ICU can emerge either as a rapid primary episode caused by an acute reduction in perfusion after shock, hemorrhage, resuscitation or low output septic shock or as a late-onset form of hepatic injury emerging secondarily to multiple septic episodes and medical treatment strategies.⁴ New onset of liver dysfunction is a frequent finding in critical ill patients and significantly contributes to increased

morbidity and mortality. Early recognition and subsequent therapy of the underlying conditions are still the therapeutic cornerstones.⁵

Hepatic dysfunction is traditionally considered to indicate poor outcome in critically ill patients, but no large systematic investigation into its exact incidence and prognostic relevance has been performed in different population groups like children, adolescents and adults.⁶

As there is paucity of data regarding hepatic dysfunction in patients admitted in PICU we have done a prospective study to evaluate the prevalence, patterns and significance of liver function tests in critically ill patients admitted in PICU.

METHODS

A hospital based prospective study was conducted in a tertiary care hospital in North India from June 2012 to May 2013.

Objectives of this study were to evaluate the prevalence and patterns of deranged liver function tests (LFT's) at admission in critically ill children and to study the correlation of LFT's to the morbidity and mortality in critically ill children admitted in PICU.

Inclusion criteria

All critically ill children between 1-17 years age group admitted in Paediatric Intensive Care Unit were included.

Exclusion criteria

Any children with pre-existing conditions that would have deranged their baseline liver function such as

- Chronic / acute primary liver disease
- Children < 1yr of age
- Metabolic disorder

- Obesity
- Readmission in ICU

The study was approved by the Institutional Ethics Committee (IEC). A written informed consent was taken from the parent (mother/father/legal guardian) before enrolment into the study.

The liver function tests of each patient admitted in PICU were requested on days 1, 3 and 7 of admission as a part of biochemical ICU profile during the study period and recorded on a predesigned pro forma. Day 1, 3 and 7 were chosen to analyse LFT pattern distributed over the sickness period. The LFT panel included ALT, AST, ALP, serum bilirubin, serum albumin, PT and INR. Age wise normal reference range for liver function tests from standard books were used in the study to analyse the values.^{7,8} The pattern of LFT on the day of admission to PICU was reported. The relationship between clinical factors (that is requirement of inotropic support or ventilator support or usage of antibiotics for more than 3 days) during the first 48 hours of ICU stay and the final outcome of the patient were compared with the LFT panel on day 1 and day 3 of hospitalization. The association between day 7 LFT and final outcome of patients was also explored in the patients who survived until day 7.

Statistical analysis

Using Chi-square analysis. A p value of <0.05 was taken as significant.

RESULTS

During the study period, 101 patients aged 1-17 years admitted to PICU were included.

50.49% (51) were males and 49.5% (50) were females. Majority of the patients belonged to 2-5 years age group (35.6%). 7-day mortality was 25.7% (27/101) (Table 1).

Table 1: Demographics and clinical data for patients admitted in PICU between June 2012 to May 2013.

Age Groups	All Patients		Discharged		Mortality		Discharged with residual deficits	
	Males	Females	Males	Females	Males	Females	Males	Females
12-24 months	12 (11.8%)	4 (3.9%)	8 (12.5%)	1 (1.56%)	4 (14.8%)	2 (7.4%)	0	1 (10%)
25-60 months	20 (19.8%)	16 (15.8%)	16 (25%)	11 (17.1%)	3 (11.1%)	2 (7.4%)	1 (10%)	3 (30%)
6-11 years	12 (11.8%)	13 (12.8%)	9 (14%)	5 (7.8%)	2 (7.4%)	6 (22.2%)	1 (10%)	2 (20%)
12-17 years	7 (6.9%)	17 (16.8%)	5 (7.8%)	9 (14%)	2 (7.4%)	6 (22.2%)	0	2 (20%)
Total	101		64 (63.3%)		27 (26.7%)		10 (9.9%)	

*Total number of patients 101, divided into age groups

The pattern of LFT on the day 1 of admission depicted abnormal PT and serum albumin levels in large proportion of children however, most of the values were between 1-2 times the upper limit of normal. Serum

bilirubin was normal in most of the patients on admission, however liver enzymes were equally distributed between the normal and abnormal groups (Table 2).

Table 2: Distribution of LFT values on day 1 of hospital admission.

Day 1	Normal	Abnormal	p value	1-2 x ULN	>2 x ULN	p value
AST	50 (49.5%)	51 (50.4%)	0.88	28 (27.7%)	23 (22.7%)	0.32
ALT	53 (52.4%)	48 (47.5%)	0.48	28 (27.7%)	20 (19.8%)	0.1
ALP	88 (87.1%)	13 (12.8%)	0.00	10 (9.9%)	3 (2.9%)	0.00
TSB	83 (82.1%)	18 (17.8%)	0.00	14 (13.8%)	4 (3.9%)	0.00
Alb	13 (12.8%)	88 (87.1%)	0.00	84 (83.1%)	4 (3.96%)	0.00
PT	31 (30.6%)	70 (69.3%)	0.00	62 (61.3%)	8 (7.9%)	0.00
INR	56 (55.4%)	45 (44.5%)	0.12	40 (39.6%)	5 (4.95%)	0.00

#Abnormal values are values greater than upper limit of normal for age; 1-2 x ULN is 1 to 2 times the upper limit of normal; >2 x ULN is greater than two times the upper limit of normal; TSB: Total serum bilirubin; Alb: Serum Albumin; *Abnormal serum albumin is value of serum albumin less than lower limit of normal for age

Analysing individual components of LFT on day 1 and 3 of admission showed deranged AST, ALT, serum bilirubin, serum albumin, pro thrombin time and INR had significant association with increased requirement of both

inotropic and ventilatory support during the hospital stay as well as with increased mortality rate. Only alkaline phosphatase did not show a significant association with requirement of ventilatory/inotropic support and neither with the risk of mortality (Table 3 and Table 4).

Table 3: Association of Day1 LFT with clinical events and outcome of children admitted in PICU.

LFT	Invasive ventilation		P value	Inotropic support		P value	Death		P value
	Normal	Abnormal		Normal	Abnormal		Normal	Abnormal	
AST 1	12 (24%)	26 (50.9%)	0.00	26 (52%)	40 (78.4%)	0.00	8 (16%)	19 (37.25%)	0.01
ALT 1	13 (24.5%)	25 (52%)	0.04	27 (50.9%)	39 (81%)	0.01	8 (15%)	19 (39.5%)	0.00
ALP 1	29 (32.9%)	9 (69.2%)	0.01	55 (62.5%)	11 (84.6%)	0.21	18 (20.9%)	9 (68.2%)	0.00
TSB 1	22 (26.5%)	16 (88.8%)	0.00	49 (59%)	17 (94.4%)	0.00	15 (18%)	12 (66.6%)	0.00
Alb1	1 (7.6%)	37 (43%)	0.01	5 (35.7%)	61 (70.1%)	0.01	0	27 (30.6%)	0.01
PT 1	2 (6.4%)	36 (51.4%)	0.00	14 (45.1%)	52 (74.2%)	0.00	1 (3.2%)	26 (37.1%)	0.00
INR 1	9 (16%)	29 (64.4%)	0.00	30 (53.5%)	36 (80%)	0.00	8 (14.28%)	19 (42.2%)	0.00

#AST 1, ALT 1, ALP 1, TSB 1, S. Alb1, PT 1, INR 1-AST, ALT, ALP, TSB, S. Alb, PT, INR on day1 of admission to hospital; TSB: Total serum bilirubin; Alb: Serum Albumin

Table 4: Association of Day3 LFT with clinical events and outcome of children admitted in PICU.

LFT	Invasive ventilation		P value	Inotropic support		P value	Death		P value
	Normal	Abnormal		Normal	Abnormal		Normal	Abnormal	
AST2	8 (17.7%)	23 (48.9%)	0.00	20 (44.4%)	37 (78.7%)	0.00	2 (4.4%)	16 (47%)	0.00
ALT2	11 (22%)	20 (47.6%)	0.00	23 (46%)	34 (80.9%)	0.00	4 (8%)	14 (33.3%)	0.00
ALP2	26 (31.7%)	5 (50%)	0.29	49 (59.7%)	8 (80%)	0.3	13 (15.8%)	5 (50%)	0.02
TSB2	20 (25.9%)	11 (73.3%)	0.00	44 (57.1%)	13 (86.6%)	0.03	9 (11.68%)	9 (60%)	0.00
Al 2	3 (13.6%)	28 (40%)	0.02	8 (36.3%)	49 (70%)	0.00	0	18 (25.7%)	0.00
PT2	3 (10.3%)	28 (44.4%)	0.00	14 (48.2%)	43 (68.2%)	0.02	0	18 (31%)	0.00
INR2	8 (15.6%)	23 (56%)	0.00	23 (45%)	34 (82.9%)	0.00	2 (3.9%)	16 (39%)	0.00

§AST2, ALT2, ALP2, TSB2, Alb2, PT2, INR 2-AST, ALT, ALP, TSB, Alb, PT, INR on day 2 of admission to hospital; TSB: Total serum bilirubin; Alb: Serum Albumin

LFT parameters followed until day 7 of admission showed, a significant correlation between normal AST, ALT, serum bilirubin, pro thrombin time and INR on day

7 with a good outcome in these patients. However, those patients who were discharged with some residual deficits (neurological deficits) showed a varied result (Table 5).

Table 5: Association of Day 7 LFT with clinical outcome of children admitted in PICU.

LFT	Death		P value	Discharged		P value	Discharged with residual deficits		P value
	Normal	Abnormal		Normal	Abnormal		Normal	Abnormal	
AST3	2 (4.1%)	8 (33.3%)	0.01	43 (87.5%)	21 (50%)	0.00	3(6.2%)	7(29.1%)	0.09
ALT3	3 (5.8%)	7 (21.2%)	0.04	43 (84.3%)	21 (63.6%)	0.02	5(9.8%)	5(15.1%)	0.45
ALP3	9 (11.5%)	2 (40%)	0.12	59 (75.6%)	3 (60%)	0.60	10(12.8%)	0	1.0
TSB3	4 (5.4%)	6 (60%)	0.00	61 (82.4%)	3 (30%)	0.00	9(12.1%)	1(10%)	1.0
Alb3	0	10 (15.8%)	0.05	18 (85.7%)	46 (73%)	0.23	3(14.2%)	7(11.1%)	0.70
PT3	0	10 (20%)	0.00	30 (88.2%)	34 (68%)	0.03	4(11.7%)	6(12%)	1.0
INR3	1 (1.6%)	8 (38%)	0.00	54 (87%)	10 (47.6%)	0.00	7(11.2%)	3(14.2%)	0.70

[†]AST3, ALT 3, ALP3, TSB3, Alb3, PT3, INR 3-AST, ALT, ALP, TSB, S. Alb, PT, INR on day 3 of admission to hospital; TSB: Total serum bilirubin; Alb: Serum Albumin

There was no significant association noted between any of the parameters studied and antibiotic usage in the patients probably because most of the patients received antibiotics for more than 48hrs in view of their serious condition or patients being discharged from the hospital with residual deficits. Serum ALP levels showed varied results, this could be because of the varied source of synthesis of ALP in the body.

DISCUSSION

Our study showed that liver function tests can be an excellent predictor of prognosis in sick children and also proved to be a best indicator for predicting the risk of complications in them.

In critically ill patients, hypoxic, toxic and inflammatory insults can affect hepatic excretory, synthetic and/or purification functions, leading to systemic complications such as coagulopathy, increased risk of infection, hypoglycemia and acute kidney injury. In severe cases, hepatic encephalopathy or brain dysfunction (acute liver failure) may occur. Hence monitoring of liver function is essential in sick children.

Because of the lack of specificity of standard laboratory investigations, identifying liver injury or dysfunction in critically ill patients remains a significant challenge. In addition, the great heterogeneity of criteria used to define the consequences of liver insults increases the difficulties for the clinician to properly interpret hepatic biochemical abnormalities.⁹

Hypoxic hepatitis is the commonest form of hepatic injury in medical ICU and is proven to be strongly associated with enhanced mortality rates specially in patients requiring inotropic support.¹⁰

Kleinberg in his study tried to find a correlation between the different liver function parameters in critically patients. In spite of rather pronounced pathological findings a statistically significant correlation could only be found between SGPT and SLDH. However, his study demonstrated the importance of liver involvement in critically ill patients on the one side and the necessity of comprehensive and repeatedly performed investigations of liver function in such patients on the other side.¹¹

Some of the studies tried to look for the risk factors for the development of liver dysfunction in critically ill patients.¹² Study by Brienza et al showed that severe shock states, sepsis, mechanical ventilation with PEEP and major surgery were the critical risk factors for liver dysfunction.¹³

Most of the studies have analysed individual components of LFT to assess the prognosis in critically ill patients.¹⁴ Serum albumin was the most commonly used predictor in similar studies.¹⁵⁻¹⁷

ALP showed varied results in our study which was similar to other studies probably because the patients included were growing children and also ALP is influenced by multiple factors.¹⁸ In the literature search most of the studies done on LFT included adult patients.¹⁹

One of the studies in children by Eisenhut et al compared disease severity as judged by duration of ventilation, inotrope use and mortality in children who were ventilated for respiratory syncytial virus (RSV) positive lower respiratory tract infection (LRTI) with and without elevated transaminase levels. Study showed that duration of mechanical ventilation was significantly longer in the group with elevated transaminase level and inotrope use was also more common and all the deaths occurred in the

group with elevated transaminase levels.²⁰ However, keeping in view, the small study group further study on larger group or multicentric studies are suggested to further validate the role of various liver function test parameters as prognostic indicators in PICU.

CONCLUSION

From the present study we conclude that complete liver profile should be essential part of the biochemical profile in the patients admitted to PICU for prognostication of critically ill patients and also early liver protective measures can be considered to prevent further injury. The study setting was a tertiary care unit with significant proportion of referred patients. Doctors caring for sick patients in the peripheral hospitals should consider for early referral of the patient to higher centers based on LFT parameters which are available in most of the places, as in the present study abnormal LFT parameters suggests caution.

ACKNOWLEDGEMENTS

Author would like to pay special thankfulness, warmth and appreciation to his supervisor, Dr. Ashwani Sood for his vital support and assistance, Professor Neelam Grover, Head of the Department of Pediatrics, whose reminders and constant motivation encouraged him to meet the deadlines. Author would also like to thank all the faculty, staff members and lab technicians of Biochemistry Department, whose services turned his research a success.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Mallikarjuna A, Sood AK. Liver function tests as a prognostic indicator in Pediatric Intensive Care Unit (PICU). *Int J Contemp Pediatr* 2018;5:1031-5.