
*CHANGES OF LIVER SIZE AND ITS FUNCTION IN
CRITICALLY ILL PATIENTS AT PEDIATRIC
INTENSIVE CARE UNIT*

By

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ABSTRACT

Introduction: Critical illness may result in hepatic injury due to alterations in hemodynamic and oxygen delivery and metabolic derangements. This may result in alteration of liver size as well as impairment of important liver functions.

Aim of the study: to Study liver size changes during the period of admission into PICU and its correlation with AST, ALT and CRP.

Patients and Methods: 50 Patients were recruited from PICU at Sayed-Galal-University Hospital in the period from February to July 2020. All patients admitted to PICU were included in our study unless they did not fulfill the inclusion criteria.

- Patients were examined clinically and investigated by AST, ALT and CRP
- Clinical and laboratory Follow up weekly were done including ALT, AST and CRP.
- Pelvi-abdominal ultrasound was done when any changes of its size detected clinically.

Results: Total number of studied patients was 50, the most common indication of admission was Respiratory problems which constitute 44% followed by surgical problems about 28% while neurological problems in 16% and 12% were cardiac problems.

15 children (30%) of study patients had hepatomegaly according to age with mean liver span on admission 11.57 ± 1.9 that increased after one week to 13.37 ± 2.3 but did not show significant changes after two weeks as the mean was 13.86 ± 3.39 .

The studied patients had elevated ALT, AST and CRP above upper level of normal with percentage 58%, 56 and 62% consequently.

Conclusion: Hepatomegaly and abnormalities of liver enzymes is a common finding in PICU especially in patients suffering from pneumonia and heart failure. Patients with hepatomegaly and altered hepatic function admitted to PICU carry a bad prognosis with long hospital stay, requirement of mechanical ventilation, inotropic support and they have a high mortality rate than those without hepatomegaly.

Keywords: *Hepatomegaly, Liver enzymes, CRP, PICU.*

INTRODUCTION

In critically ill patients, liver is the main organ of metabolic arrangements which promote the production and clearance of inflammatory mediators, the scavenging of bacteria and bacterial products (e.g., endotoxin) and the synthesis of acute phase proteins (Nessler et al., 2015).

Hepatic dysfunction emerges in non-hepatic PICU patients as a complication of their critical illness. Different grades of hepatic dysfunction affect about 50% of all ICU patients (Strassburg, 2003).

Risk factors are involved including shock, sepsis, heart failure and therapy-induced hepatic dysfunction (Soultati and Dourakis, 2005).

Hepatic dysfunction emerges either early or late within the critical illness. Early hepatic dysfunction occurs within hours of the risk factor (e.g., shock). In this case hypoxic (or ischemic) hepatitis occurs as a result of acute hepato- splanchnic hypoperfusion leading to rapid elevation of hepatic enzymes. However, it is usually rapidly reversed within few days with adequate supportive treatment (Horvatits et al., 2013).

In contrast, late hepatic dysfunction, as in sepsis, is a more insidious and ominous process. It is characterized by structural and functional damage mainly due to microvascular blood flow disturbances. So, early and late hepatic dysfunctions are allied to profound alterations in global and microcirculatory liver perfusion, respectively (Kramer et al., 2007).

In most cases hepatic dysfunction starts without any noticeable changes in the patient clinical profile. Therefore, clinical suspicion of liver complication mainly depends on abnormal biochemical tests (Soultati and Dourakis, 2005).

Aims of the Work

To study liver size changes during the period of admission into PICU and its correlation with liver enzymes and CRP.

PATIENTS AND METHODS

50 Patients were recruited from PICU at Sayed-Galal-University Hospital during the period from February to July 2020. All patients admitted to PICU were included in our study unless they did not fulfill the inclusion criteria.

Inclusion Criteria:

- Both sexes are included.
- Age from 2 months up to 16 years old.
- Any cause of admission into PICU.
- Duration of study not less than 1 week.

Exclusion criteria:

- Length of stay in the PICU is less than 1 week
- Any manifestation of hepatic dysfunction as Jaundice, metabolic diseases at time of admission.
- Anatomic hepatic lesion as cyst or mass.
- Multiple organ dysfunctions.

Ethical consideration:

- Written Parent consent for the study was obtained before the study.
- Approval of the local ethical committee was obtained before the study.
- The authors declared no potential conflict of interest with respect to the research & publication of this article.
- All the data of the patient & results of the study are confidential & the patient has the right to keep it.

- The authors received no financial support for the research & publications of the article.

Method:

1. Patients were examined clinically and investigated by AST, ALT and CRP.
2. Clinical and laboratory Follow up weekly were done including ALT, AST and CRP for detection of any abnormality of liver size or its function.
3. Pelvi-abdominal ultrasound were done when any changes of liver size detected clinically.
4. Follow up of admitted study patients regarding their requirement of mechanical ventilation, inotropic support with regular measurement of liver size.
5. Statistical analysis: Data were statistically described in terms of mean standard deviation (SD), median, range and inter quartile range (IQR), or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables was done using Student t test for independent samples in comparing 2 groups of normally distributed data/ large sample and Mann Whitney U test for independent samples for

comparing not-normal data. For comparing categorical data, Chi-square (2) test was

performed. All statistical calculations were done using computer program IBM SPSS.

RESULTS

Table (1): Demographic characteristics of studied patients

		No. = 50
Age (Years)	Median(IQR)	0.79 (0.25 - 4)
	Range	0.1 – 11
Gender	Female	27 (54.0%)
	Male	23 (46.0%)
Weight (kg)	Median(IQR)	8.50 (5.4 – 16)
	Range	3.5 – 40
Weight (percentile)	Below 5 th	11 (22.0%)
	25 th	16 (32.0%)
	50 th	13 (26.0%)
	75 th	8(16.0%)
	Above 95 th	2 (4.0%)
Length(cm)	Mean ± SD	79.00 ± 24.17
	Range	52 – 143
Length (percentile)	Below 5 th	5 (10.0%)
	25 th	29 (58.0%)
	50 th	12 (24.0%)
	75 th	4 (8.0%)
Head circumference (percentile)	Below 5 th	2 (4.9%)
	25 th	21 (51.2%)
	50 th	11 (26.8%)
	75 th	7 (17.1%)

A total of 50 patients aged less than 11 years were included in our study. The median age was 0.79 years old

54% of them were female and 46% were male. The median weight was 8.5kg while the mean length was 79cm ± 24.1.

Table (2): Indications of admission of studied patients to PICU

Indication of admission	No.	%
Respiratory	22	(44.0%)
Pneumonia	14	28.0%
Asthma exacerbation	2	4.0%
Broncholitis	4	8.0%
pleural effusion	2	4.0%
Neurological	8	(16.0%)
intractable fits	2	4.0%
Encephalitis	3	6.0%
HTN encephalopathy	2	4.0%
GuillinBaree syndrome	1	2.0%
Cardiac	6	(12.0%)
H.F	5	10.0%
CHD with dehydration	1	2.0%
Surgical	14	(28.0%)
Intestinal obstruction	4	8.0%
Intussusception	3	6.0%
Appendicectomy	3	6.0%
Exploration	3	6.0%
Diaphragmatic hernia	1	2.0%

This table shows that the most common indication of admission was respiratory problems which constitute 44% followed by

surgical problems about 28% while neurological problems in 16% and 12% were cardiac problems.

Table (3): Frequency of hepatomegaly and its consistency among studied patients

		No. = 50	%
Liver span	Normal (group I)	35	70.0%
	Hepatomegaly (group II)	15	30.0%

This table shows 30% of study patients had hepatomegaly.

Table (4): Follow up of liver span and consistency in group II

Liver span	Mean \pm SD	Range
ON admission	11.57 \pm 1.96	7.5 – 15
After 1 week	13.37 \pm 2.37	10 – 18
After 2 weeks	13.86 \pm 3.39	9 – 18
Consistency	NO 15	%
Soft	1	6.7%
Firm	14	93%

This table shows that the mean liver span 11.5 ± 1.9 as base

line while 1 week later 13.3 ± 2.3 and after 2 weeks 13.8 ± 3.3 .

Table (5): Frequency of abnormalities of liver enzymes and CRP in studied patients

		No. = 50
ALT (I.U.L)	Normal (10-50)	21 (42.0%)
	High >50	29 (58.0%)
AST(I.U.L)	Normal (10-40)	22 (44.0%)
	High >40	28 (56.0%)
CRP (mg/L)	Negative <6	19 (38.0%)
	Above upper level of normal >6	31 (62.0%)

This table shows that 58% of studied patients had ALT above upper level of normal while 56% had AST above upper level of

normal and 62% of our study patients had CRP above upper level of normal.

Table (6): Comparison between both groups regarding vital data on admission

		Group I No. = 35	Group II No. = 15	Test value	P-value	Sig.
Respiratory Rate	Mean \pm SD	45.11 \pm 10.66	53.20 \pm 11.19	-2.42•	0.01	S
	Range	30 – 68	28 – 71			
Heart Rate	Mean \pm SD	126.43 \pm 9.06	143.93 \pm 16.93	-4.76•	0.0	HS
	Range	109 – 143	110 – 167			
Temperature	Mean \pm SD	37.67 \pm 0.48	39.90 \pm 9.26	-1.43•	0.16	NS
	Range	36.8 – 39	36 – 73.3			
Blood pressure	Hypotensive	0 (0.0%)	1 (6.7%)	6.42*	0.27	NS
	10 th	2 (5.7%)	2 (13.3%)			
	25 th	13 (37.1%)	8 (53.3%)			
	50 th	16 (45.7%)	4 (26.7%)			
	50 th	2 (5.7%)	0 (0.0%)			
More 95 th	2 (5.7%)	0 (0.0%)				
Oxygen Saturation on room air	Mean \pm SD	92.29 \pm 3.63	84.60 \pm 5.23	5.99•	0.0	HS
	Range	82 – 98	77 – 97			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value < 0.01: highly significant (HS), *:Chi-square test; •: Independent t-test

This table shows that there is statistically significance difference regarding respiratory

rate, heart rate and oxygen saturation between the two groups.

Table (7): Comparison between both groups regarding abnormalities of liver enzymes and CRP

		Group I No. = 35	Group II No. = 15	Test value	P- value	Sig.
ALT (I.U.L)	Mean \pm SD	48.97 \pm 31.07	78.87 \pm 9.44	-3.63•	0.00	HS
	Range	11 – 99	66 – 97			
Normal		21 (60.0%)	0 (0.0%)	15.52*	0.00	HS
High		14 (40.0%)	15 (100.0%)			
AST (I.U.L)	Mean \pm SD	38.23 \pm 25.89	73.33 \pm 14.23	-4.92•	0.00	HS
	Range	11 – 90	49 – 89			
Normal		22 (62.9%)	0 (0.0%)	16.84*	0.00	HS
High		13 (37.1%)	15 (100.0%)			
CRP (mg/L)	Mean \pm SD	15.09 \pm 9.48	15.33 \pm 8.09	-0.09•	0.93	NS
	Range	4 – 32	6 – 32			
Negative		15 (42.9%)	4 (26.7%)	1.17*	0.28	NS
Above upper level of normal		20 (57.1%)	11 (73.3%)			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value < 0.01: highly significant (HS).

*:Chi-square test; •: Independent t-test

This table shows that there is highly significant difference

between both group regarding ALT and AST.

Table (8): Comparison between both groups regarding Mechanical ventilation support, inotropic support, stay at PICU and mortality

		Group I No. = 35	Group II No. = 15	Test value	P- value	Sig.
Mechanical ventilation support	Not ventilated	34 (97.1%)	5 (33.3%)	24.92*	0.00	HS
	Ventilated	1 (2.9%)	10 (66.7%)			
Inotropic support	Not need	33 (94.3%)	5 (33.3%)	21.39*	0.00	HS
	Need	2 (5.7%)	10 (66.7%)			
Stay at PICU days)	Mean \pm SD	10.23 \pm 2.96	18.07 \pm 6.63	-5.82•	0.00	HS
	Range	7 – 21	10 – 30			
Death	Survival	33 (94.3%)	6 (40.0%)	18.03*	0.00	HS
	Expired	2 (5.7%)	9 (60.0%)			

P-value >0.05: Non-significant, (NS); P-value <0.05: Significant (S); P-value < 0.01: highly significant (HS) *:Chi-square test; •: Independent t-test

This table shows significant correlation between hepatomegaly and mechanical

ventilation support, inotropic support and long duration of stay at PICU.

Table (9): Follow up of ALT and AST in group II

	Mean±SD	Range	P-value (ANOVA test)
ALT			
On admission	78.87 ± 9.44	66 – 97	0.04 (S)
After 1 week	96.60 ± 12.87	79 – 123	
After 2 weeks	105.71 ± 26.81	65 – 125	
AST			
On admission	73.33 ± 14.23	49 – 89	0.02 (S)
After 1 week	85.13 ± 14.93	55 – 123	
After 2 weeks	86.29 ± 21.86	49 – 112	

In group II there was statistically significant increase

in ALT and AST between Baseline vs 1st week only.

DISCUSSION

Abnormalities of liver functions in PICU are either a cause or a complication of the critical illness and ICU admission. The liver is the maestro of several metabolic and inflammatory processes during the critical illness. Therefore, hepatic dysfunction whether primary or secondary could hasten the worsening of the patient condition leading to significant morbidity and mortality (Newton et al., 2014).

Patients with liver disease may need an intensive care due to ALF or acute decomposition of CLD including ACLF. In these cases the indication of ICU admission are usually bleeding, encephalopathy or infection (Kaur et al., 2013).

On the other hand, those are critically ill patients who are not known to have a liver disease and yet they have abnormal LFTs during their critical illness. Those patients with abnormal LFTs are usually overlooked and underestimated (Horvatits et al., 2013).

ICU patients could have more life-threatening conditions, especially those including the respiratory and cardiovascular systems, which withdraw the doctor's attention from the apparently less important abnormal LFTs. For this reason several studies have emerged that focus on the significance of abnormalities of liver functions in the ICU morbidity and mortality. These studies were mostly on adult patients and to our

knowledge no similar studies were done in PICU. The last study addressing this problem in the pediatric population was in 1992 by **Jacquemin et al.**, who studied hypoxic liver injury in patients with circulatory shock. In our study we focused on the frequency, risk factors and outcomes of abnormalities of liver size and function in critically ill children. Thirty percent of our patients (15/50) had hepatomegaly, fifty eight percent had elevated ALT and fifty-six percent had elevated AST. The incidence of liver function abnormalities among critically ill adult patients varied in different studies. **Kramer et al., in 2007** reported an 11% incidence of early liver function affection; within 48 hours of admission to ICU. Another study by **Thomson et al., in 2009** found that 61% of patients admitted to ICU had abnormal LFTs (ALT, GGT, AP and bilirubin) after excluding patients with primary liver disease. Recently **in 2017, Saloojee et al.** reported a 21.3% incidence among critically ill trauma patients.

As the ICU bed availability usually influence ICU admission decisions, ICUs with low bed availability may tend to deny admission for patients who are deemed too sick to benefit from

admission (**Robert et al., 2015**). Patients with decompensated chronic liver disease are sometimes considered too sick to benefit from intensive care; a concept opposed by **Alam et al. (2016)** who reported a 60% survival in children with Acute-on-chronic liver failure. So admission decisions influenced by bed scarcity, which may result in refusal of patients likely to benefit from admission out of concern that the ICU would then be unable to admit a patient in greater need of critical care, is still a debate (**Wightman et al., 2014**). Twenty-two percent of our study group were malnourished. Malnutrition was associated with prolonged LOS on univariate analysis but not associated with mortality so malnourished children were slower to recover. Similarly, **in 2015 Bagri et al.**, from India reported a 51.2% prevalence of malnutrition among PICU admissions and a significant association between malnutrition and prolonged LOS > 7 days but not associated with increased mortality. In another study from Brazil, 45.5% of PICU patients were malnourished which caused them to have a longer LOS in PICU (**De Souza Menezes et al., 2012**). A study from a developed country like UK by **Prince et al., in 2014**, reported a much less

prevalence of malnutrition among PICU admissions (18%) compared to developing countries and it was an independent risk factor for mortality. In our study, malnutrition was not significantly associated with abnormalities of liver functions or size, suggesting that those underweight children are not more susceptible to develop abnormal liver functions or hepatomegaly than well-nourished children during PICU admission due to critical illness. In general, malnutrition has an impact on the development of multiple organ dysfunction syndromes and its related mortality (**Fink and Kissoon, 2017**).

Twenty-two patients (44%) had respiratory problems which constitute the most common indication of admission, but surgical problems constitute the next common indication of admission as it represent (28%) of our studied patients.

About respiratory problems pneumonia represent the most common respiratory problems need PICU admission as it represent (28%) of our studied patients.

Four patients (8%) had evidence of sepsis; in contrast to other study as **de Souza et al., in 2016** which reported an incidence

of sepsis of 42.6% in 21 PICUs in 5 South America countries. Incidence of sepsis in other studies was much lower as 8.2% (**Scott L. Weiss et al., 2015**), 14.9% (**Pedro et al., 2015**) or 17.3% (**Khan et al., 2012**). The percentage of culture proven infection in other studies was 30% (**Pedro et al., 2015, Khan et al., 2012**). Sepsis was also associated with mortality and prolonged LOS in the study by (**Ruth et al., 2014**). The prevalence of sepsis among patients increased with prolonged hospital stay, reaching 100% among patients who stayed in PICU for > 30 days. This implies that prolonged LOS predisposes to PICU-acquired infection and sepsis. This is because patients were exposed to several interventions and multiple skin pricks for sampling during their long LOS which could have made them more susceptible to sepsis. In a study by **Porto et al., in 2012**, the presence of an invasive device and longer time of hospitalization in PICU are from the major risk factors for the acquisition of nosocomial infection in PICU patients. In our study, the incidence of abnormalities of liver size and functions in patients with sepsis was 13.3% of all patients with hepatomegaly with elevated ALT and AST. Sepsis was significantly associated with

abnormal liver functions and hepatomegaly more than patients without sepsis. In sepsis, the liver is an important mediator of host defense but is also at risk for injury itself (**Ghosh et al., 1993**). Pre-existing liver dysfunction is a risk factor for the progression of infection to sepsis. On the other hand, liver affection that comes after sepsis is an independent risk factor for multiple organ dysfunction and sepsis-induced mortality (**Yan et al., 2014**).

Regarding patients, who experienced cardiovascular events, account 33% of patients who had hepatomegaly and abnormalities of AST and ALT. Hepatic affection was significantly associated with all forms of cardiovascular events including heart failure, shock and cardiac arrest. In these situations, the liver is affected due to decreased blood flow to the liver leading to diminished oxygen delivery, especially in the presence of sepsis that increases oxygen demand and impairs its extraction by the hepatocyte (**Birrer et al., 2007**). Inotropes were used in 24% of patients, of which 83% had hepatic affection either abnormalities of liver function or increase of its size. So the use of inotropes was significantly associated with hepatic affection. The principal response of the

hepatic vascular bed to vasopressors is vasoconstriction. Noradrenalin and adrenaline divert blood flow away from the mesenteric circulation and decrease microcirculatory blood flow in the gastrointestinal tract despite increased perfusion pressure and increased systemic blood flow (**Fuhrmann et al., 2011**). Furthermore, experimental data suggest that catecholamine may deteriorate hepatocellular function by induction of an inflammatory response syndrome (**Aninat et al., 2008**).

CONCLUSION

Hepatomegaly and abnormalities of liver enzymes is a common finding in PICU. Patients with primary hepatic dysfunction admitted to PICU have a high mortality rate. Cardiovascular events, pneumonia, sepsis, M.V support and the inotropic support had positive correlation with occurrence of hepatomegaly and abnormalities of liver enzymes. Also long duration of stay at PICU have positive correlation with occurrence of hepatomegaly and abnormalities of liver enzymes.

RECOMMENDATION

- Changes of liver size and liver enzymes in PICU should be considered seriously as a predictor of poor prognosis.

- Every effort should be made to prevent and to treat these conditions underlying liver affection as sepsis, pneumonia and Cardiovascular events.
- More study needed and should be considered for more details about pathogenesis and pathology of liver affection.

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التغيرات فى حجم الكبد ووظائفه فى الرعايه المركزه للاطفال

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المقدمة: قد يؤدي المرض الخطير الى اصابه الكبد بسبب التغيرات فى توصيل دوره الدمويه والاكسجين، والتشوهات الأيضية والأثار الثانويه للالتهاب الجهازى والعلاجات الطبيه، وقد يؤدي هذا الى ضعف وظائف الكبد المهمه بما فى ذلك ازالة السموم من الدم والمشاركه فى الاستجابه المناعيه وتخليق البروتينات، والوسطاء الالتهابيون، والصفراء، وقد يؤدي نقص هذه الوظائف الى تفاقم المرض الخطير، مما يخلق حلقه مفرغه، والمراسه والوفيات والتكلفه المرتبطه بالخلل فى وحدة العنايه المركزه المرتفعه.

الهدف من البحث: دراسة التغيرات فى حجم الكبد خلال فترة القبول فى الرعايه المركزه للاطفال وارتباطها مع انزيمات الكبدوبروتين سى التفاعلى.

مادة البحث وخطوات العمل: وقد أجريت الدراسة على 50 مريضاً من 6 اسره فى مستشفى سيد جلال الجامعى فى الفتره من فبراير الى يوليو 2020، تم تضمين جميع المرضى الذين تم حجزهم فى الرعايه المركزه للاطفال فى دراستنا مالم يلتقوا بمعايير الاقصاء.

تم فحص المرضى من الباطن سريريا وتم عمل وظائف كبد وبروتين سى التفاعلى اسبوعيا للكشف عن حدوث اى تغير فى حجم الكبد ووظائفه.

تم اجراء موجات فوق صوتيه فى منطقة البطن والحوض عندما يتم اكتشاف اى تغير فى حجم الكبد سريريا.

وقد أظهرت هذه الدراسة النتائج الآتية: كان العدد الاجمالى للمرضى 50 وكان المؤشر الاكثر شيوعا للحجز هو مشاكل الجهاز التنفسى التى تمثل 44% تليها مشاكل جراحية حوالى 28% بينما كانت المشاكل العصبية فى 16% و 12% مشاكل فى القلب.

30% من مرضى الدراسة لديهم تضخم فى الكبد و 58% لديهم ارتفاع فى الانين امينوترانسفيراز و 56% لديهم ارتفاع فى الاسبارتات امينوترانسفيراز و 62% لديهم ارتفاع فى بروتين سى التفاعلى فوق المعدل الطبيعى.

خلاصة البحث: استنتجا مما سبق نجد نجد ان تضخم الكبد والتغيرات فى وظائفه نتيجة مشهوره فى الرعاية المركزه للاطفال.