The need for liver transplant in a sample of Iraqi children with chronic liver disease

La necesidad de un trasplante de hígado en una muestra deniños iraquíes con enfermedad hepática crónica

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Abstract

Liver disease is one of the major causes of hospitalization and mortality in children. A wide spectrum of disorders including developmental abnormalities, infections, metabolic and genetic disorders can lead to liver disease in pediatric patients. Determination of its etiology is important for treatment, prevention of progressive liver damage, family counseling and prioritizing liver transplantation. We aimed to assess the need of Iraqi children with chronic liver disease and acute liver failure for liver transplantation and to discover the commonest indication for liver transplant in Iraqi children. **Patients and methods**: A retrospective study of patients' files and records from early neonatal period up to 14 years of age with end stage liver disease and patients with acute liver failure that carried out in welfare teaching hospital and the gastroenterology center of the medical city, during a period from 1st of August 2019 to 30th of April 2021. A pre-constructed data collection sheet, consisted of two sections: the first section gathering the socio-demographic data (age, sex, residence (province). The second section included the clinical data; etiology and lab investigations results. Mean pediatric end stage liver diseases (PELD) score was calculated to all cases depending on their age, gender, growth parameter (height and weight) and laboratory investigations results (Total serum bilirubin level, albumin, international normalized ratio {INR}). Statistical analysis was performed using SPSS software version 23. Result: A total number of 369 patients were enrolled, the mean ± sd age was 4.8±4 years, ranging between 2 month and 14 years, 39% of patients were between age 3-10 years. 212 male patients and 157 female patients. 27.4% of patients had progressive familial intrahepatic cholestasis (PFIC), 15.8% had chronic liver disease, 12.5% had Wilson disease, 9.2% had glycogen storage disease, 7.9% had autoimmune hepatitis, 6% had drug induced, 4.5% had biliary atresia. 73.7% had PELD score less than 11 and PELD score significantly associated with present of complication like ascites and encephalitis and had positive correlation with liver enzyme and PT with negative correlation with age and vit D. **Conclusion**: there was a high percentage of Iraqi children who were complaining of end stage liver disease and acute liver failure and in need for liver transplantation and a significant proportion of studied children were need to frequent evaluation and follow up according to pediatric end stage liver disease score and there were a problem in our country because of the lack of some specific tests needed to determine the etiological diagnosis and lack of a program of hepatic transplantation.

Keywords: pediatric liver transplant, acute liver failure, end stage liver disease, PELD score, ascites, hepatic encephalopathy

Resumen

La enfermedad hepática es una de las principales causas de hospitalización y mortalidad infantil. Un amplio espectro de trastornos que incluyen anomalías del desarrollo, infecciones, trastornos metabólicos y genéticos pueden provocar enfermedades hepáticas en pacientes pediátricos. La determinación de su etiología es importante para el tratamiento, la prevención del daño hepático progresivo, el asesoramiento familiar y la priorización del trasplante de hígado. Nuestro objetivo era evaluar la necesidad de trasplante de hígado de los niños iraquíes con enfermedad hepática crónica e insuficiencia hepática aguda y descubrir la indicación más común de trasplante de hígado en niños iraquíes. Pacientes y métodos: Estudio retrospectivo de los archivos y registros de pacientes desde el período neonatal temprano hasta los 14 años de edad con enfermedad hepática en etapa terminal y pacientes con insuficiencia hepática aguda que se llevó a cabo en el hospital universitario asistencial y el centro gastroenterología de la ciudad médica. durante un período comprendido entre el 1 de agosto de 2019 y el 30 de abril de 2021. Una hoja de recolección de datos preconstruida, constaba de dos secciones: la primera sección recopilaba los datos sociodemográficos (edad, sexo, residencia (provincia). La segunda sección incluía los datos clínicos; la etiología y los resultados de las investigaciones de laboratorio. La puntuación media de las enfermedades hepáticas en etapa terminal pediátrica (PELD) se calculó para todos los casos en función de su edad, sexo, parámetro de crecimiento (altura y peso) y resultados de las investigaciones de laboratorio (nivel de bilirrubina sérica total, albúmina, razón internacional normalizada (INR). El análisis estadístico se realizó con el software SPSS versión 23. Resultado: se inscribió un total de 369 pacientes, la edad media ± de 4,8±4 años, con un rango de 2 meses a 14 años, 39% de los pacientes tenían entre 3 y 10 años. 212 pacientes varones y 157 mujeres. 27,4% de los pacientes tenían colestasis intrahepática familiar progresiva (PFIC), 15,8% tenían enfermedad hepática crónica, 12,5% tenían enfermedad de Wilson, 9,2% tenían enfermedad de almacenamiento de glucógeno, 7,9% tenían hepatitis autoinmune, 6% tenían fármacos inducidos, 4,5% tenían atresia biliar. El 73,7% tenía una puntuación PELD menor de 11 y una puntuación PELD asociada significativamente con la presencia de complicaciones como ascitis y encefalitis y tenía correlación positiva con las enzimas hepáticas y PT con correlación negativa con la edad y la vitamina D. Conclusión: hubo un alto porcentaje de niños iraquíes que se quejaban de enfermedad hepática en etapa terminal e insuficiencia hepática aguda y necesitaban un trasplante de hígado y una proporción significativa de los niños estudiados necesitaban ser evaluados con frecuencia y siga de acuerdo con la puntuación de la enfermedad hepática en etapa terminal pediátrica y había un problema en nuestro país debido a la falta de algunas pruebas específicas necesarias para determinar el diagnóstico etiológico y la falta de un programa de trasplante hepático.

Palabras clave: trasplante de hígado pediátrico, insuficiencia hepática aguda, enfermedad hepática en etapa terminal, puntaje PELD, ascitis, encefalopatía hepática

Introduction

Liver transplantation is a life-saving procedure for patients with chronic end stage liver disease and selected patients with acute liver failure when there are no available medical and surgical treatment options[1,2]. Liver transplantation is considered to be an accepted treatment method for children and adults with survival rates approaching 90%[3]. Before transplantation, patients with advanced liver disease usually died within months to years. These patients now have the opportunity for extended survival with excellent quality of life after liver transplantation[4]. Liver transplantation has been very successful in treating children with end-stage liver disease, and offers the opportunity for a long healthy life. Organ scarcity, which is the main limitation to the full exploitation of transplantation is being overcome thanks to innovative surgical techniques, and all children in need, even the youngest, today have the chance of being transplanted, with almost no waiting list mortality. Split-liver and living-donor transplantation have contributed to reversing a situation in which, during the 1980s and 90s, children had greater waiting list mortality compared to that of adult patients. Several years ago, the main focus of care of children with end-stage liver disease was to find a liver transplant, but today, the main interest is in long-term follow-up, with prevention of immunosuppression-related complications and promotion of as normal growth as possible. The history of pediatric liver transplantation has clearly shown that success is dependent on strict and integrated collaboration between referring pediatricians, pediatric transplant hepatologists, transplant surgeons, nurses, transplant coordinators, psychologists and social workers. Everybody involved has the task of bringing a cure to a population of pediatric patients who present some of the most challenging clinical[4].Since February 2002. PELD score was specifically developed for children with end-stage liver disease, and statistically validated in a large multicenter database[5]. This new score is a simple and standardized model which deemphasizes the waiting time as allocation criteria, and relies on objective, clinical (age, growth retardation) and biochemical (bilirubin, albumin, INR) parameters. Within the PELD system, waiting time is used only to rank patients with identical PELD scores within a particular blood group: in this latter instance, when a patient moves to a higher PELD score, a new waiting time clock starts, whereas

if the patient moves to a lower PELD score, time accumulated at higher score is included[6]. PELD score proved to be an important prognostic marker for survival and is a useful tool where individual assessment of the severity of liver disease and prioritization on the waiting list cannot be made in other ways and this scoring was used in assessment of children before liver transplant and these scoring systems are frequently used in other countries[7,8]. For suitable treatment of liver disease in children the need for early diagnosis etiological definition and good evaluation should be emphasized. Thus, the aim of this study is to report the causes of liver cirrhosis and evaluate its complications in children from Iraq.

Methods

A retrospective study carried out in welfare teaching hospital and the gastroenterology center of the medical city, during a period 1st of August 2019 to 30th of April 2021. A total number of 369 patients from early neonatal period up to 14 years of age with end stage liver disease and patients with acute liver failure, had been enrolled in this study. Data were collected using patients' files and records. A pre-constructed data collection sheet, consisted of two sections the first section gathering the socio-demographic data (age, sex, residence (province), weight and height). The second section included the clinical data; etiology and lab investigations results. PELD score was calculated to all cases depending on their age, gender, growth parameter (height and weight) and laboratory investigations results (Total serum bilirubin level, albumin, international normalized ratio). After the data had been collected, then checked for any errors or inconsistency, it was transferred into a computerized database software in which Microsoft excel was used. Statistical analysis was performed using SPSS (statistical package for social sciences) software version 23, Descriptive statistics were presented as mean ± standard deviation and as frequencies and proportions (percentages). Chi-square test was used to find the significance of comparison for frequencies and proportions. correlation test to find association between two continuous variables and when the value of Pearson correlation coefficients between 00-0.19 mean a very weak, 0.20-0.39 "weak", 0.40-0.59 "moderate", 0.60-0.79 "strong" and 0.80-1.0 "very strong, level of significance (P. value) ≤ 0.05 considered as significant correlation.

Results

A total of 369 patients with end stage liver disease were included, the mean ± sd age was 4.8±4 years, ranging between 2 month and 14 years. the demographic characters were shown in table-1- and the cause of end stage liver disease were shown in table 2.

Table 1. Demographic characters of study patients

Variable		No. (n=369)	Percentage (%)
Age (Years)	< 1	77	20.9
	1 - 3	96	26.0
	3 - 10	144	39.0
	> 10	96	14.1
Gender	Male	212	57.5
	Female	157	42.5
Residence	Baghdad	172	46.6
	Other province	197	53.4

Table 2. Causes of end stage liver disease

Causes of end stage liver disease	Number(n=369)	Percentage (%)
PFIC	101	27.4
Wilson disease	46	12.5
Chronic liver disease	58	15.8
Glycogen storage disease	34	9.2
Autoimmune Hepatitis	29	7.9
Drug induced	22	6.0
Biliary atresia	20	5.4
HCV	18	4.9
Alagille syndrome	16	4.3
Cystic fibrosis	12	3.3
Galactosemia	9	2.4
HBV	4	1.0

The PELD score of studied patients was shown that majority of patients had PELD score <11, figure 1 and the distribution of PELD score according to causes of and stage liver disease shown in table 3.

Figure 1. Distribution of studied patients among PELD score.

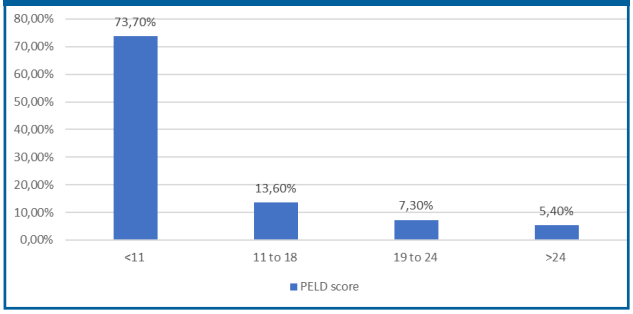

Table 3. The PELD score according to causes of and stage liver disease.

Causes of end stage liver disease	PELD score			
	< 11 (%) n= 272	11 - 18 (%) n= 50	19 - 24 (%) n= 27	> 24 (%) n= 20
PFIC	72 (71.3)	16 (15.8)	8 (7.9)	5 (5.0)
Wilson disease	41 (89.1)	4 (8.7)	0 (0)	1 (2.2)
Chronic liver disease	43 (74.1)	6 (10.3)	6 (10.3)	3 (5.2)
Glycogen storage disease	32 (94.1)	1 (2.9)	1 (2.9)	0 (0)
Autoimmune Hepatitis	24 (82.8)	2 (6.9)	3 (10.3)	0 (0)
Drug induced	13 (59.1)	6 (27.3)	0 (0)	3 (13.6)
Biliary atresia	14 (70.0)	4 (20.0)	1 (5.0)	1 (5.0)
HCV	16 (88.9)	1 (5.6)	1 (5.6)	0 (0)
Alagille syndrome	4 (25.0)	5 (31.3)	3 (18.7)	4 (25.0)
Cystic fibrosis	7 (58.3)	2 (16.7)	2 (16.7)	1 (8.3)
Galactosemia	4 (44.4)	1 (11.2)	2 (22.2)	2 (22.2)
HBV	2 (50.0)	2 (50.0)	0 (0)	0 (0)

Table 4. Association between PELD score and certain information

Variable		PELD Score				P - Value
		< 11 (%) n= 272	11 - 18 (%) n= 50	19 - 24 (%) n= 27	> 24 (%) n= 20	
Gender	Male	157 (74.1)	31 (14.6)	11 (5.2)	13 (6.1)	0.263*
	Female	115 (73.2)	19 (12.1)	16 (10.2)	7 (4.5)	
Ascites	Yes	25 (35.7)	11 (15.7)	18 (25.7)	16 (22.9)	0.001*
	No	247 (82.6)	39 (13.0)	9 (3.0)	4 (1.3)	
Encephalitis	Yes	1 (16.7)	1 (16.7)	3 (50.0)	1 (16.7)	0.001*
	No	271 (74.7)	49 (13.5)	24 (6.6)	19 (5.2)	

* chi-square test, significant ≤0.05.

The PELD score associated with present of complication (ascites and encephalitis) while shown no association with gender, table 4.

The PELD score had moderate negative correlation with age and VIT D and moderate positive correlation with SGPT, SGOT and PT, table 5.

Table 5. Correlation between PELD score and certain characters.

Variable	PELD Score	
	R	P - Value
Age	-0.31	<0.001
SGPT	0.384	<0.001
SGOT	0.373	<0.001
PT	0.543	<0.001
Vit D	-0.17	<0.001

Discussion

Liver transplantation is considered to be the standard of care for children and adults with end stage liver disease[9]. However, the promise of transplantation is limited by the availability of donor organs for transplant and availability of resources. There is little epidemiological information regarding etiology of liver cirrhosis in children and it's change over time in Iraq, so this study done to study the common etiological causes for liver disease in children. The mean age in current study was 4.8 years with male predominant this similar to other study like Oman study[10] where the mean age was 5 years and similar to Annual Data Report: Liver of OPTN/SRTR 2011[11] And this can be explained by, this age group is the main age when most of liver diseases are quite evident clinically or diagnosed by laboratory investigations.

The causes for end stage liver disease in this study were PFIC in 101 (27.4%) ,followed by chronic liver disease and Wilson disease, this in line of Oman study[10] that found progressive familial intrahepatic cholestasis (30%) was the most common causes of liver cirrhosis, and in comparison to the North American children, where the biliary atresia was the most common indication for liver transplant[12] also in Indian study[13], the indication that came first was

biliary atresia(36%) followed by autoimmune liver disease (7.5%), followed by PFIC(5%) and in also in Tunisian study[14], biliary causes was the most frequent causes. The Biliary atresia was clearly dominating than other liver diseases in both studies, this can be explained by the biliary atresia being a liver disease which presents in the early neonatal period and the transplant procedure can be done in these countries as early as the infant start to have critical liver impairment condition, while in Iraq, the patient would keep on waiting for a period of time which is difficult to predict related to the financial hardship that limits sending the patients with end stage liver disease for liver transplantation, so patients who had Kasai operation had the chance to be transplanted surviving longer periods, while PFIC is a chronic liver disease that gives the chance for the patient to survive longer time with better chances for transplant.

When PELD score was assessed and estimated for all patients, a wide range of variation was found that ranged from (-11) (the least value) to (50) (the highest value), and this wide range agreed with a study in USA[15], which concludes that the PELD score has no minimal or maximal value and can range from a negative number to a high positive number. When the calculated PELD score was categorized into 4 categories (according to values), it had been found that 140 (65.7%) of the cases had had a PELD score <11, which again agreed with the USA study[15] but still those patients with low PELD score might have other health related unstable conditions that necessitate the need for liver transplants.

The group of PELD score more than or equal to 25 need immediate liver transplant, while those with PELD (19-24) need follow up every one month, and those in between (11-18) need to be evaluated every six months, and the last group (<11) their PELD must be followed up every one year. In this study there was no significant finding when the comparison was done between the patient's PELD score the sex, this may be explained by, that the PELD score is not affected by the patient gender. The development of complication like ascites and hepatic encephalopathy have a significant impact on the prognosis of patients with liver disease, the accumulation of ascites is a result of portal hypertension, vasodilatation, and hyperaldosteronism. Hypoalbuminemia is an additional risk factor for ascites and this also proved in our finding by the significant association of present of complication with PELD score.

When the PELD score was correlated with age there were a negative correlation between PELD score and age, this may be due to the fact that smaller age group had a 2 score points added to their real score, also could be attributed to the early affection of growth parameters by the impact of chronicity of the liver disease upon younger age groups.

Chronic liver dysfunction reflects hemodynamic changes on patients with end stage liver disease[16], liver function tests may be helpful in determining the short-term prognosis among groups of patients awaiting liver transplantation[17], and that was evident in this study, by the positive correlation between SGPT, SGOT and PT with PELD score.

Children with chronic liver disease are at increased risk for malnutrition, with abnormal defective metabolism of Fat-soluble vitamins, and low levels of some of these vitamins may play a prognostic role[18].

This study showed a significant negative correlation (the higher the PELD score the lower the level of the Vitamin), this agreed with other studies finding, like USA study[19] that found Associations between vitamin D and liver function and liver fibrosis in patients with biliary atresia and China study[20] that have demonstrated a high frequency of vitamin D deficiency in children who require liver transplantation.

Conclusions

1-PFIC and Wilson disease were the most common causes of end stage liver disease in this study.

2-The development of complication like ascites and hepatic encephalopathy have a significant impact on the prognosis of patients with liver disease.

3- Liver function tests may be helpful in determining the short-term prognosis among groups of patients awaiting liver transplantation.

4- This study showed a negative value (reversed correlation) between vit D and PELD score.

This study also has several limitations. First, retrospective cohort study and some patients were lost to follow-up, which may have resulted in selection bias. Large multicenter, prospective studies are needed to test and verify our findings. Second, the scores were merely determined at admission, so we were not able to evaluate the dynamic predictive role of the scores.

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