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Clinical Profile Of A Group Of Iraqi Children With Transplanted Liver

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ABSTRACT

Back ground: Iraq is a developing country with limited medical resources, especially those services related to organ transplant, particularly liver transplant. With high incidence of consanguineous marriages leading to inherited diseases of liver and many metabolic diseases with liver involvement.
Aim of study: To highlight the liver transplant outcome in a sample of Iraqi children.
Methods: Since 2011 ministry of health started assessing children in need for liver transplant as the last resort for survival, sending them abroad to highly specialized liver transplant centers in India and Turkey. Twenty-two patients who had underwent living donor's liver transplant from May of 2011 till May of 2019 were included. The patient's data records were evaluated retrospectively. The medical profile and outcome of patients and overall survival was analyzed.
Results: All transplanted livers were from living relative donors, mothers in 63.6% children, while father's donation in 36.4% children, the mean age at time of transplant was (4.23±3.2 years), males were 17\22 (77.3%) while females were 5\22 (22.7%). Mean pediatric end stage liver diseases (PELD) score before the operation was 18.64-+6.7. The indication for liver transplant were progressive familial intrahepatic cholestasis in 8 \22 (36.4%) children, followed by biliary atresia 6\22 (27%), Complications following transplant operation included rejections in 8 children (5 acute 22.7%, 3 chronic 13.6%), followed by 4 hematological (18%), 2 (9%) biliary complications, 2 (9 %) dermatological and 2 nephrological and 2 right sided diaphragmatic hernia, while malignancy, hepatic collection and chronic diarrhea occur in one child. One-year Overall survival rate was 100%, 3- and 5-years overall survival was 90 %.
Conclusion: Liver transplant in children has of very rewarding outcome with 90% five years overall survival rate with significant growth and physical improvement.

Keywords: Pediatric liver transplant, end stage liver diseases, PELD score, living donors.

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INTRODUCTION

Liver transplantation has been the standard of care for the past three and one-half decades for children with acute liver failure and chronic end-stage liver disease. Over this time pediatric liver transplant recipients have benefited from significant advancements in surgical techniques, organ procurement, pre and post-operative medical management and immunosuppression[(1)]. Liver transplantation proved being very successful in managing children with end-stage liver disease, and gives the chance for a long healthy life[(2)]. Organ shortage, which is the main obstacle to the full exploitation of transplantation, is being solved thanks to innovative surgical maneuvers, and all children who need, even very young age groups, nowadays have the chance of transplantation, with no significant waiting list mortality [(3)]. In the young population the common indications for Liver transplantation are Biliary atresia, metabolic disease, acute liver failure, and cholestasis. In the age group of 1 to 5 years, malignant liver tumors become the 4th indication for liver transplantation. In the population aged 11 to 17 years, noncholestatic cirrhosis is the most common cause for liver transplantation[(4)]. Referral to liver transplantation depends on the child's clinical circumstances: emergent in acute liver failure or acute decompensation, urgent in progressive disease, or anticipatory. The timing of referral may depend on disease progression. In some metabolic diseases, early referral may offer the benefit of avoiding multisystemic complications and irreversible organ damage[(5)]. The primary goal of the evaluation process is to identify appropriate candidates for liver trasplantation and establish a peritransplantation plan. Children have distinct diseases, clinical susceptibilities, physiologic responses, as well as neurocognitive and neurodevelopmental features that distinguish them from adults and differ within the pediatric age group. The goal of the evaluation process is to confirm the indication for transplantation, discuss alternative treatments, exclude contraindications; discuss complications associated with end-stage liver disease (ascites, pruritus, portal hypertension, malnutrition, vitamin deficiencies, and delayed growth), and optimize pretransplant medical therapy and immunizations (as live vaccines are relatively contraindicated post-LT)[(6)].A timely referral to transplant evaluation is a crucial step to assure good success in both early and long-term phases. Such a referral does not necessarily always lead to transplantation, rather it empowers the transplant team to rule out any treatable causes that can avoid transplantation and to put in place a detailed and supportive care plan in case transplant is needed. It is imperative to refer a patient to the transplant center as soon as acute liver failure or an irreversible liver disease is diagnosed. The healthier a patient is at presentation to the transplant center, the better are the chances to optimize their status and get them if needed, to transplantation in a timely fashion[(7)]. In Iraq, there were no

liver transplantation centers and the role of medical physician in liver disease clinic where to received, diagnosed and followed up of children and the aim of this study was to highlight the liver transplant outcome in a sample of Iraqi children.

PATIENTS AND METHODS

This is a cross sectional study which was included twenty-two children with different end stage liver diseases and sent abroad for liver transplantation in highly specialized liver transplant centers in India and Turkey, through the period between May 2011 and May of 2019. Their medical files were reviewed retrospectively. The child age at transplantation, gender, blood group, donor consanguineous, weight and height Z score before operation and after one and three year was measured where the formula for calculating the z-score is $z\text{-}score = (X-m)/SD$, in which X is the observed value (height, weight or BMI), m and SD are the mean and standard deviation value of the distribution corresponding the reference population according to the WHO [8], the causes of their end stage liver disease were pointed and The severity of liver disease was classified according to PELD score(pediatric end stage liver disease)[9]. The children scheduled visits to the outpatient liver diseases clinic were also reviewed where the type of complication, fallow up period and outcome were recorded. Statistical analysis was performed with IBM SPSS version 23. Categorical variables are presented as frequency and percentage, while continuous variables are presented as mean and standard deviation (SD), ANOVA test uses to find difference in the weight and height score after one and three years of transplantation. As appropriate, Kaplan-Meier survival analysis was carried out to estimate overall survival which was the time from the date of the first diagnosis to the date of the death of last fallow up. The level of statistical significance was set to <0.05.

RESULTS

the baseline Demographic characteristics of patients enrolled in this study show that males were more dominant than females within the ratio of 3.4:1, the mean age of children was4.23±3.2 years and the main blood group for recipients was group A+ and O+ (27.3 %) for each group. Parent's consanguinity was +ve in (77.3%) the rest characters were in table 1.

Table -1- Baseline Demographic characteristics of the patients.

Baseline characteristics of children		No.	%
Gender	Male	17	77.3
	Female	5	22.7
Age at transplant (Mean±SD)		4.23±3.2 years	
Child Blood group	A+	6	27.3
	B+	4	18.2
	AB+	5	22.7
	O+	6	27.3
	O-	1	4.5
Weight Z score (Mean±SD)		-2.09±1.1	
Hight Z score (Mean±SD)		-3.08±1.3	
Parent's consanguinity	+ve	17	77.3
	-ve	5	22.7
PELD score (Mean±SD)	18.64±6.7		

Figure -1- show that Progressive Familial Intrahepatic Cholestasis (PFIC) is the most common cause of liver disease that leads to the need for liver transplantation in the current study 8/22 (36.4%) of patients followed by biliary atresia 6/22 (27.3%).

As shown in figure 2 all donor were living persons (not from cadaver) and the living mother was the most common donor (63.6%) then living father (31.8%) and only (4.6%) for both as donors for the same patients. Regarding to the complications, we found that rejection was the most common (34.8%), then hematological complication (17.4%) (Table 8).

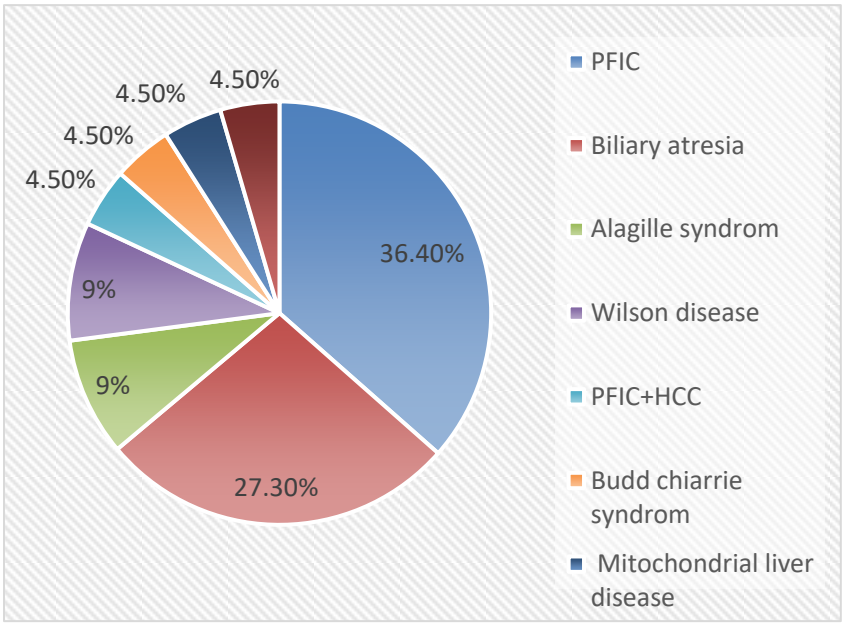

Figure -1-Causes of liver disease

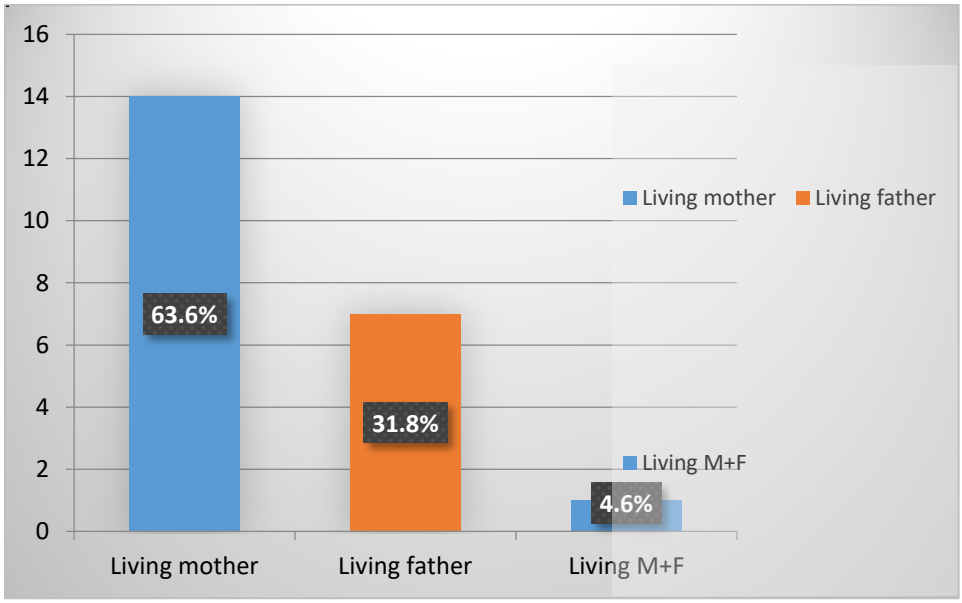

Figure -2- Relation of donor to recipient children.

Table-2- Type of complication occur after transplantation.

Variables			No.	%
No complication			10	45.5%
Complication			12	54.5%
Type of complication	Rejection	Acute	5	22.7%
		Chronic	3	13.6%
	Biliary		2	9%
	Hepatic collection		1	4.5%
	Hematological (Megaloblastic anemia, iron deficiency anemia, autoimmune hemolytic anemia)		4	18%
	Malignancy (Non-Hodgkin Lymphoma)		1	4.5%
	Surgical (right sided Diaphragmatic Hernia)		2	9%
	Dermatological (Nail dysplasia, vitiligo)		2	9%
	Nephrology (calcinosis, renal tubular acidosis)		2	9%
	Associated disease (CD+GH def.)		1	4.5%
	Chronic diarrhea		1	4.5%

CD= ……., GH def=……

The mean Weight and height Z score was significantly increase for the children after transplantation(p=0.0001), table -3-.

Table -3- Difference in weight and height Z score for children after one and three years of transplantation.

		Number	Mean ±S D	P value
Weight Z score	Baseline	22	-2.09±1.14	0.0001*
	After one year	18	-0.3±1.15	
	After 3 years	14	-0.55±1.51	
Height Z score	Baseline	22	-3.08±1.35	0.0001*
	After one year	18	-1.58±1.16	
	After 3 years	14	-1.65±0.83	

*ANOVA test, significant p value ≤0.05. The median follow-up of the study population was 3 years (range 0.5–7.5 years), Overall 6-month and 1,2, 3 and 5 years survival rates were 100%, 100%, 100%, 90% and 90%, respectively, figure -3-

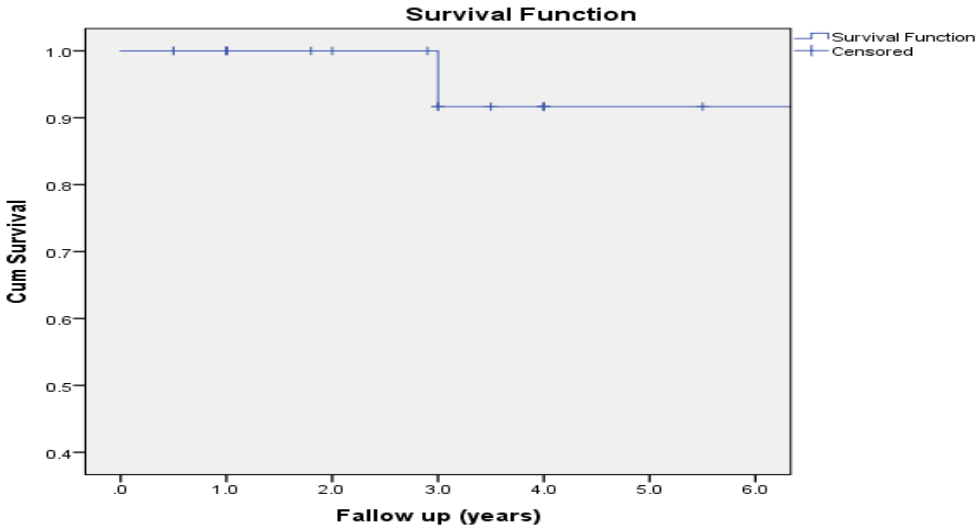

Figure -3- Kaplan- Meier survival analysis for overall survival.

DISCUSSION

Iraq is a middle east country with highly efficient medical and paramedical staff but rather retarded medical services and medical infrastructures, these services include the liver transplantation centers (for adults and pediatrics). The children with chronic liver diseases are received, diagnosed and followed up was occur in the Children Welfare Teaching Hospital (CWTH) which is the tertiary teaching medical centers, where this study had been conducted, usually the PELD score is estimated for each child with end stage liver disease, then referred to the liver transplant committee in the ministry to decide sending the patient abroad to highly specialized liver transplant centers. This might take months to years to be validated according to the financial situation of the ministry, some patients were lost while waiting. This study shows that from the total of 22 children The age with mean±SD age 4.23+_3.2 years, this in line of Turkish study[10],which was performed on 61 children (median age 3.8 years, range 0.5–16years). the male gender dominated on the females gender (77.3% ,22.7%) respectively, this in line of an Indian study[11], which include200 patient with male gender predominance of 60%. 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(12, 13). The indications for liver transplant according to their frequency in this study were PFIC in 8 (36.4%) ,followed by biliary atersia in 6 (27.3%) ,in comparison to the North American children, where the biliary atresia remains the most common indication for liver transplant (14) also in Indian study (11),the indication that came first was biliary atresia(36%) followed by autoimmune liver disease (7.5%) ,followed by PFIC(5%). 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 Kassie 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. All patients received living donor's liver transplant and mothers were the main donors for children this may related to societal factors and religious traditions. Most frequent complication was the graft rejection 8(36%), five were acute (22.7%) and 3(13.6%) chronic rejections, in comparison with the Indian study (11) which reveals that 25% of the patients had had acute rejections, where in turkey study[10] the rate of acute rejections was 39.3% and chronic rejections was 7.4%,results among the three studies are nearly identical.While surgical complications were (17.4%), biliary complications in this study constituted 8.7% and 8.7% right diaphragmatic hernia, hematological complications were iron deficiency, autoimmune hemolytic anemia and megaloblastic anemia in 17.4%, In this study no patient had infection after coming back from the specialized transplantation centers ,this can be explained by the patient long time hospital stay and close follow up and proper treatment in those centers before sending back home.All patients in this study, had significant increment in weight and height after the first year of transplantation with significant statistical value in patients with and without complications, this can be explained by the fact that those complications were managed and corrected in all the patients without any delay having no impact on the growth, except one patient who died due to chronic rejection with severe malabsorption and renal tubular acidosis. The other patient who died, had very poor compliance to immunotherapy, developed generalized lymphadenopathy ending up with Malignancy (Non-Hodj. Lymphoma). The Survival rate in this study was high as those reported for North American and European children[15, 16]. which suggested an increase in timely patient referrals, improvements in surgical techniques, improved operative and perioperative patient management, immunosuppressive treatment, an increased good identification of early complication and good fallow up.

CONCLUSION

Liver transplant in children has of very rewarding outcome with 90% five years overall survival rate with significant growth and physical improvement.

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