International Journal of Celiac Disease, 2021, Vol. 9, No. 1, 12-15
Available online at http://pubs.sciepub.com/ijcd/9/1/4
Published by Science and Education Publishing
DOI:10.12691/ijcd-9-1-4

In a Time of Pandemic: Predictors for Post-transplant Respiratory Complications

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Received January 03, 2021; Revised January 18, 2021; Accepted January 21, 2021

Abstract *Introduction*: Biliary atresia is commonly associated with malnutrition and failure to thrive. Very few studies have been published on the impact of preoperative malnutrition on post-transplant outcomes in these children. *Material and Methods*: 110 children underwent living donor liver transplantation from January 2003 to March 2013. Pre-transplant malnutrition was defined according to z scores for the weight for age and height for age as per who definition. Patients having both Z score of < -2 were compared with the control group. Statistical analysis was done using SPSS version 21 (IBM). *Results*: 39 children out of 110 were having z score for the weight for age < -2. There was no statistical difference between PELD score, graft weight, GRWR, intraoperative blood loss between to groups. 22 out of 39 patients in malnourished group developed clavein grade 3, grade 4 complications and 32 patients out of 71 in the control group developed clavien grade 3 grade 4 complications. (p= 0.318). The overall mortality rate was 4.5% and mortality rates in the malnourished vs control group were respectively 7.69% and 2.81% (p= 0.278). A total of 14 patients developed postoperative pulmonary complications. Pulmonary complications were significantly high in the malnourished group. p=0.003. *Conclusion*: Preoperative malnutrition is associated with a high postoperative pulmonary complication rate in liver transplantation for biliary atresia.

Keywords: *biliary atresia, liver transplants, pulmonary complication*

Cite This Article: Bhavin Vasavada, "In a Time of Pandemic: Predictors for Post-transplant Respiratory Complications." *International Journal of Celiac Disease*, vol. 9, no. 1 (2021): 12-15. doi: 10.12691/ijcd-9-1-4.

1. Introduction

Biliary atresia is the most common indication of liver transplantation in the pediatric population [1,2]. Timely intervention such as Kasai hepatoportoenterostomy can halt the progression of the disease, however despite this procedure progressive hepatic damage continues in the majority of patients and 70-80% of patients require liver transplant within the first two years of life [3,4,5]. Malnutrition and growth retardation are significant problems in biliary atresia patients. Decreased oral intake, early satiety due to organomegaly, fat malabsorption, and increased energy expenditure due to a hypermetabolic state all likely contribute to malnutrition in biliary atresia patients [6]. However, there are few studies on the impact of pre-transplant nutrition status on the post-transplant outcomes. The purpose of our study was to evaluate the impact of pre-transplant malnutrition on the post-transplant outcomes of the patients.

2. Material and Methods

2.1. Study Design

Data of all the patients who underwent living donor liver transplants for biliary atresia between January 2003 and April 2013 were collected and retrospectively analyzed. We included all the patients who have z scores for weight/age and height /age -2 as a study group. In end-stage liver disease due to ascites, edema weight for age alone may not be the accurate indicator of nutrition status. So, to avoid confusion we selected patients having both the z scores = -2 as inclusion criteria. (Wasted and shunted as per who definition) Z score was calculated as percenters of disease control and prevention charts. (http://www.cdc.gov/growthcharts/zscore.htm). Liver transplant outcome was measured as clavien dindo classification grade 3 and grade 4 complications and overall mortality [7]. These outcomes were compared between the malnourished and control groups.

2.2. Statistical Analysis

Statistical analysis was done using the chi-square test for categorical variables and Mann Whitney U test for continuous variables. P-value < 0.05 was considered to be statistically significant. Multivariate analysis was done using the MANOVA method. Statistical analysis was done using SPSS version 21(IBM).

3. Results

110 patients underwent living donor liver transplant from January 2003 to April 2013.39 patients out of 110 were having Z score of weight by age and weight by

height -2.characteristics of both the group is described in Table 1. Patients' characteristics are described in Table 1. Malnutrition group had significantly higher median PELD (p=0.001) and Large size grafts (GRWR >2.5) were significantly more common in the malnutrition group as we do not use reduced grafts.

Table 2 mentions various complications in the two groups. 22 patients suffered from 43 complications in the malnutrition group whereas 32 patients suffered from 60 complications in the control group. There was no statistically significant difference between overall complication rates. (P=0.318). As can be seen from Table 2 respiratory complications were significantly more common in the malnourished group. (p=0.003) We included ARDS and postoperative pneumonia and atelectasis in the respiratory complication group.3 patients died in the malnutrition group and 2 patients in the no malnutrition group. There was no statistically significant difference between both groups in overall mortality rates. (p=0.278).

3.1. Univariate Analysis of Respiratory Complications

On Univariate analysis, we analyzed the association between various factors like age at transplant, sex, PELD score, CTP score, Large for size graft, Operative blood loss, Operative duration, Previous Kasai procedure, Timing of Kasai procedure. Respiratory complications were significantly associated with PELD score (p=0.049), and Z scores -2(p=0.003). Large for size graft showed borderline P value of 0.069 and as large for size graft was significantly more common in malnutrition group, we included it in multivariate logistic regression.

3.2. Multivariate Analysis: (Table 3)

As shown in Table 3 on multivariate analysis only Z score-2 (both weight/age and height/age) independently predicted respiratory complications with a p-value of 0.03.

Table 1. Patients characteristics

Factors	Malnutrition/growth Failure group (Z= -2)(N=39)	Non-malnutrition Group (N=71)	P-value
Age (month) (Median)(Range)	13(2-63)	17(3- 180)	P=0.290
Sex	21 male 18 female	34 male 37 females	P=0.456
CTP	8.5(5-15)	8(5-17)	P=0.815
PELD	18(8-32)	11(5-25)	P=0.001
Type of graft	38-left lateral,1=left	59=left lateral,3=left,6=right	P=0.137
Large for size grafts (GRWR >2.5)(n)	34/39	35/71	P=0.000
Intra operative blood loss(ml)	205(200-2400)	200(100-1500)	P=0.716
Primary transplant (without previous kasai procedure)	3	3	P=0.459
Age at kasai (month)	60(2-120)	60(2-140)	P=0.959
Transplant after second kasai procedure. (N)	5	5	P=0.337

Table 2. Complications observed during the study period. Early graft dysfunction was defined as bilirubin greater than 20 on POD 7

Factors	Malnutrition/growth Failure group (Z= -2)(N=39)	Non malnutrition Group (N=71)	P value
Early Graft dysfunction (N)	4	4	0.451
Bile leak (N)	2	2	0.549
Bile duct stricture	1	1	0.675
Biopsy proven Acute cellular rejection	5	10	P=0.798
Bleeding requiring re-exploration	2	2	P=0.598
Renal dysfunction (requirement of dialysis)	0	2	P=0.276
Sepsis	3	8	P=0.474
Multi organ dysfunction	3	1	P=0.1
Abdominal compartment syndrome	0	1	P=0.443
Respiratory complications (ARDS, Postoperative pneumonia)	10	4	P=0.003
Hepatic artery thrombosis	3	9	P=0.382
Portal vein thrombosis/stenosis	5	5	P=0.390
Hepatic vein outflow obstruction	1	0	P=0.195
Retransplant	0	1	P=0.436
Intestinal perforation	1	3	P=0.598
Prolonged ascites	3	7	P=0.606
Over all complications (no of patient)	22	32	P=0.318
Mortality	3	2	P=0.278

Table 3. Multivariate analysis for respiratory complications

Factors	P-value
Peld score	.325
Zscore less than 2	.03
Large-for-size graft	.733

3.3. Mortality

3 patients died in the malnutrition group and 2 patients in the no malnutrition group. There was no statistically significant difference between both groups in overall mortality rates. (p=0.278).

4. Discussion

Pre-transplant malnutrition is associated with worse post-transplant outcomes. Barthes et al showed that worse pre-transplant height/age score was associated with increase postoperative hospital stay and hospital costs. [8] Estela in his review stated that malnutrition and growth failure are considered to be important risk factors for poor outcomes following liver transplantation [9]. Shepherd et al suggested that declining nutrition status in the waiting period of transplant adversely affected outcomes [10]. Sullivan et al suggested that in malnourished children pre-transplant parenteral nutrition gives post-transplant outcome comparable to the non-malnourished children [11]. The body-weight of children with liver disease can be modulated by many factors, including ascites so the weight/age ratio can be confounded by various factors such as ascites, edema in end-stage liver disease. So, to avoid this confusion and to accurately define pre-transplant malnutrition we defined malnutrition as both heights by age and weight by age -2 [wasted and shunted as per who definition] to accurately measure malnutrition.

We compared post-transplant complications and mortality between the malnutrition or growth failure group and the normal group. Complications like bile leak, stricture, bleeding complications, graft dysfunction, Acute cellular rejection, renal dysfunction, sepsis, hepatic artery thrombosis, portal vein stenosis and thrombosis, outflow obstruction, multi-organ dysfunction, abdominal compartment syndrome, re-transplantation, intestinal perforation, prolonged ascites, etc. were similar between malnutrition and non-malnutrition group. In our study, the malnourished group had a significantly higher rate of pulmonary complications (p=0.003). We included complications like ARDS, post-transplant pneumonia, and atelectasis in pulmonary or respiratory complications. Figueiredo et all suggested in adult liver transplant preoperative malnutrition is associated with an increased risk of post-operative infections, respiratory complications, and a prolonged stay in the ICU [12]. Poor nutrition induces muscle weakness and muscle cachexia. Prolonged and severe muscle cachexia involving the respiratory muscles may increase postoperative respiratory complications [13].

We also analyzed factors like age at transplant, sex, the timing of previous Kasai procedure, no of Kasai procedure, PELD score, CTP score, Large for size graft, blood loss during surgery, duration of surgery, type of graft for their association with postoperative pulmonary complications. On univariate analysis, PELD score and Z score = -2 were significantly associated with respiratory complication. As mentioned above we added Large for size graft in multivariate analysis, as it was significantly different between the two groups. On multivariate analysis Z score = -2 independently predicted post-transplant respiratory complications. (P-value =0.022).

Neto et al in their study of 430 pediatric liver transplants suggested that height by an age z score of -2 was associated with poor patient and graft survival [14]. Derusso et al showed that after pretransplant weight deficit is associated with late patient mortality (>1 year) [15] and Soltys et al showed that the baseline z score is related to late growth retardation [16].

This study shows that preoperative optimization of nutritional status may help in getting better outcomes post-transplant in pediatric liver transplants for biliary atresia. However, this study has several limitations, as it is a retrospective study so inherent bias with any retrospective study also applies to this study. Pulmonary complications depend on many aspects like fluid overload; anesthetic management etc., accurate collections of these data on the retrospective study are always not possible.

5. Conclusion

Pre-transplant malnutrition and growth failure are associated with worsened outcomes in biliary atresia patients undergoing living donor liver transplantation. Pre-transplant malnutrition independently predicts post-transplant pulmonary complications. Preoperative optimization of nutrition status might improve outcomes in biliary atresia patients undergoing living donor liver transplantation.

Conflict of Interest

All the authors have no conflict of interest.

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