PROSPECTIVE COHORT STUDY OF THE RENAL OUTCOME IN OLT PATIENTS- A PRELIMINARY OBSERVATIONAL STUDY

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ABSTRACT

BACKGROUND

Postoperative Acute Renal Injury (ARI) is a serious clinical problem in Orthotopic Liver Transplantation (OLT). There are currently no standard criteria for the evaluation of patients with AKI or Chronic Kidney Disease (CKD) requiring Liver Transplantation (LT). The present study is taken up to fill up the lacunae. What is the use of MELD in predicting the outcome of OLT and renal function?.

The aim of our study is to determine the association of various pretransplant risk factors, especially creatinine including the MELD score on patient renal function after OLT.

MATERIALS AND METHODS

A prospective, observational study of 35 consecutive liver transplantation patients including all patients who have been worked up for OLT and who underwent liver transplantation have been included. Patients who are previously diagnosed with CKD have been excluded. Preoperative AKI is defined as S. creatinine >1.2 mg/dL, postoperative AKI is defined as a persistent rise of 50% increase or more of the S. creatinine (S. Cr).

RESULTS

Total number of patients in the present study were (n=35), mean creatinine before liver transplantation was 1.0 ± 0.6 mg/dL. Serum creatinine 1 month, 3rd month and 6th month post transplantation was 0.8 ± 0.4 mg/dL, 0.9 ± 0.4 mg/dL and 1.03 ± 0.5 mg/dL, respectively. Males in the study were 34 (97.1%), total number of females were 1 (2.9%). Cadaver transplantation was done in 21 patients (60%). Living donor transplantation was done in 14 patients (40%). Median MELD score was 25. There was no significant change in the serum creatinine range at follow up in patients who had preop creatinine of 1. Those with creatinine of >1.2 mg/dL and labelled as having HRS were found to have follow up creatinine varying between 1.3-4.5 mg/dL. The overall post-LT patient survival was 88% at 1 year, total of 4.1% underwent CVVHDF and 2 patients died in the group. Remaining 2 patients are not dialysis dependent.

CONCLUSION

In this preliminary observation, there is a progressive rise in creatinine among patients who had a baseline creatinine of around 1 mg/dL and a higher MELD score in the pretransplant situation. Even without TAC toxicity, sepsis or underlying comorbidities. The group with low MELD and low creatinine seems to be related to better health on one side, but the other group with high creatinine and higher MELD have abnormal values are possibly related to preoperative conditions, also the donor and also the duration of the transplant surgery.

KEYWORDS

Creatinine, Liver Transplantation, MELD, Sepsis.

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BACKGROUND

Pretransplant renal failure is commonly reported to be a poor prognostic indicator affecting survival after LT. However, whether the impact of renal failure on patient outcome varies according to the aetiology of the underlying liver disease is largely unknown.[1] Studies on comparative assessment of progressive renal dysfunction pre and post LT are controversial.

Recent findings- Liver transplants are allocated by the MELD score- A number heavily weighted by the serum creatinine. The serum creatinine value varies depending upon the laboratory where it is measured is different between genders without a correction factor in MELD and is generally inaccurate as a marker of kidney function in liver failure. Criteria for dual transplantation vary between programs and there is no official oversight of the practice.

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Up to 6.5% of simultaneous transplant candidates on dialysis at listing discontinue dialysis before transplant.[2] Patients with advanced liver disease. Hecker, Sherlock, Pepper and Vessin (1950) observed that renal damage is completely reversible after liver transplantation.[3]

Postoperative AKI occurred in 60.5% of patients- R-class, 23.5%; I-class, 21%; and F-class, 16%.[4] Serum creatinine prior to liver transplantation is one of the most significant predictors of post-liver transplantation ESRD.[5] Therefore, MELD, which was implemented to minimise pre-LT waitlist mortality maybe shifting mortality to the post-transplant period by assigning a higher priority to patients with renal insufficiency.[6]

Objectives

The aim of our study is to determine the association of various pre-transplant comorbidities, MELD score and serum creatinine on patient's renal function after OLT.

MATERIALS AND METHODS

A prospective, observational study of 35 consecutive liver transplantations. All patients have a S. creatinine of 6 months. N=8 patients have completed 2 yrs. follow up, N=16 have completed 1 year follow up rest are still being followed up.

Inclusion Criteria- All consecutive patients admitted for liver transplantation.

Exclusion Criteria- Patients with acute liver failure needing liver transplantation.

Preoperative AKI is defined as S. creatinine >1.2 mg/dL, postoperative AKI is defined as a persistent rise of 50% increase or more of the S. creatinine (S. Cr).

RESULTS

Total number of patients in the present study were (n=35), Table 1 shows the mean age was 47.31 ± 14.8 yrs., mean creatinine before liver transplantation was 1.0 ± 0.6 mg/dL at 1 month post transplantation was 0.8 ± 0.4 mg/dL at 3 months 0.9 ± 0.4 mg/dL and at 6 months post-transplantation was 1.03 ± 0.5 mg/dL. Males in the study were 34 (97.1%), total number of females were 1 (2.9%). Table 2 shows cadaver transplantation was done in 21 patients (60%). Living donor transplantation was done in 14 patients (40%). Most patients (n=30) had high MELD ranging between 18-43 and 25 of them had HRS type II. There were only 5 patients with a MELD score of <18 of which 2 were children, 1 had progressive familial cholestasis and the other child had type 1 hyperoxaluria, respectively. Table 3 showing the outcome in Live Donor (LD) and Cadaver Donor (CD) LT. Out of the 21 patients in CD group, there was 1 (4.8%) death. Among 14 in LD group, there was 3 (21.4%) death. P value of the outcome among the group was 0.12, which was not significant.

Table 4 shows the mean age between CD group (n=21) was 51.48 ± 11.2 yrs. compared to LD group (n=14), which was 41.07 ± 17.6 yrs., the p value is statistically significant. The mean pretransplant creatinine, bilirubin, INR, creatinine at 1st month, 3rd month, 6th month post-transplant and MELD score between CD group (n=21) compared to LD group (n=14) was statistically insignificant.

Comorbidities included type 2 diabetes mellitus in 6 patients and systemic hypertension in 4 patients. One patient had CMV reactivation. Overall, case fatality was 4 out of 35, all of them occurred in the high MELD group. Cause of death was CMV (1), GVHD (1), persistent HRS (1) and sepsis (1).

There was no significant change in the serum creatinine range at follow up in patients who had preop creatinine of 1. Those with creatinine of >1.2 mg/dL and labeled as having HRS were found to have follow up creatinine varying between 1.3-4.5 mg/dL. This finding is after discounting for TAC toxicity and serious comorbidities. This observation is clinically important and needs to be kept in mind when high-risk patients (high MELD) group. This needs to be substantiated in larger studies with careful analysis of comorbidities and drug toxicity. This is consistent with the observation in the literature.

Total number of patients in the present study were (n=35), among them 25 patients where CLD with HRS type II. One patient had AB blood group, 1 patient underwent CKLT and died due to CMV infection, one patient had GVHD and died, one patient had HCC, one patient had type I HRS and intraoperative CVVHD was done for 7 patients for acidosis and fluid balance. One patient had progressive familial intrahepatic cholestasis, one patient had fulminant hepatic failure due to rat poison intake, one patient had Wilson's disease and two patients had sepsis with delayed graft function, six patient had diabetes and four patients had hypertension. 4.1% underwent haemodialysis. The overall post-LT patient survival was 88% at 1 year with stable graft function. Total of 4.1% underwent CVVHDF and two patients died in the group. Remaining two patients are not dialysis dependent.

Parameters	Mean	Std. Deviation
Age	47.31	14.8
Creatinine	1.06	0.68
Bilirubin	6.63	6.38
INR	3.1840	2.06
Creatinine 1	0.84	0.42
Creatinine 3	0.94	0.47
Creatinine 6	1.03	0.50
MELD	25.63	7.92

Table 1. Showing Various Parameters in the Study

Transplant	Sex	Total	Chi-square	
Female	**Male**			
Cadaver Donor (CD)	0	21	21	**p-value**
0.0%	100.0%	100.0%		
Live Donor (LD)	1	13	14	
	7.1%	92.9%	100.0%	
	Total	1	34	35
Table 2. Showing Various Parameters in the Study				

*Statistically significant.

Transplant	Outcome	Total	Chi-square	
Dead	**Alive**			
CD	1	20	21	**p-value**
4.8%	95.2%	100.0%		
LD	3	11	14	
	21.4%	78.6%	100.0%	
	Total	4	31	35
Table 3. Showing the Outcome in Live Donor (LD) and Cadaver Donor (CD) LT				

Variables	Tx	N	Mean	Std. Deviation	P-Value
Age	CD	21	51.48	11.2	0.040**
LD	14	41.07	17.6		
Creatinine	CD	21	1.15	0.78	
LD	14	0.93	0.49		
Bilirubin	CD	21	6.58	5.53	0.960
LD	14	6.70	7.71		
INR	CD	21	2.76	1.36	
LD	14	3.82	2.75		
Creatinine 1	CD	21	0.87	0.44	0.385
LD	14	0.73	0.44		
Creatinine 3	CD	21	0.79	0.36	
LD	14	0.89	0.74		
Creatinine 6	CD	21	0.96	0.60	0.543
LD	14	843	0.55		
MELD	CD	21	25.3	6.8	
LD	14	26.0	9.6		
Table 4. Showing Variables in the Study between the Two Groups CD and LD					

** Statistically significant.

DISCUSSION

AKI is a common and important complication of OLT representing a major cause of morbidity and mortality in the postoperative period.[7] AKI has been associated with an eight-fold increase in mortality risk, prolonged stay in the intensive care unit and higher hospital costs.[8,9] Although, mortality rates with AKI after OLT have been reported as high (45.1-67%), patients with AKI can have a good prognosis with a recovery rate of 97%.[10,11] Previous studies have demonstrated preoperative renal injury,[12] recipient age, male sex, HCV, preoperative hypertension, diabetes mellitus, red blood cell transfusion,[13] use of vasopressors, overexposure to CNI[14] and hypoalbuminaemia as risk factors for postoperative AKI.[15]

The results from this study show that there was no significant change in the serum creatinine range at follow up in patients who had preop creatinine of 1 mg/dL. Those with creatinine of ≥1.2 mg/dL and labeled as having HRS were found to have follow up creatinine varying between 1.3-4.5 mg/dL. This finding is after discounting for TAC toxicity and serious comorbidities. Age is a significant covariate in the univariate analysis, but not in multivariate model.[6] This observation is clinically important and needs to be kept in mind when high-risk patients (high MELD) group. This needs to be substantiated in larger studies with careful analysis of comorbidities and drug toxicity. This is consistent with the observation in the literature.

Because creatinine is one of the components of MELD, one would expect a higher incidence of post-LT CKD in the MELD era.[6] The definition of CKD has evolved in the past few years. In fact, the Kidney Disease Outcome Quality Initiative of the National Kidney Foundation on CKD does not consider serum creatinine alone as a sufficient criterion for staging CKD. EGFR was determined using the 4-variable equation of the Modification of Diet in Renal Disease (MDRD) study group. Data collected for donors included age, sex, race, BMI, terminal liver enzymes, terminal total bilirubin and whether the OLT derived from a non-heart beating donor.

Transplant-related data include type of induction therapy, initial immunosuppression, cold ischaemia time, warm ischaemia time and liver allograft function.[16]

Iglesias J et al[17] hypothesised that most patients with pretransplant renal dysfunction will not experience a rapid decline in the Glomerular Filtration Rate (GFR) post-OLT to necessitate consideration for kidney transplantation even in the setting of calcineurin inhibitor-based immunosuppression. Among the 23 patients with duration of renal dysfunction, 12 weeks, the only significant predictors of GFR 20 mL/minute post-OLT were the presence of diabetes mellitus and serum creatinine at the time of transplant. Early transplantation of OLT candidates with renal dysfunction had a salutary effect on intermediate-term renal function in agreement with Iglesias J et al.[17]

Utsumi M[4] Bilbao I et al[18] hypothesised that the implementation of the Model for End-Stage Liver Disease (MELD) scoring system intended to prioritise patients with more severe pretransplantation liver disease in general and worse pretransplantation renal function in particular would improve posttransplant renal function in patients with pretransplant renal dysfunction.

Postoperative AKI occurred in 60.5% of patients- Risk-class, 23.5%; injury-class, 21%; and failure-class, 16%.[4] Serum creatinine prior to liver transplantation is one of the most significant predictors of post liver transplantation ESRD.[5] Therefore, MELD, which was implemented to minimise pre-LT waitlist mortality maybe shifting mortality to the posttransplant period by assigning a higher priority to patients with renal insufficiency.[6]

8 and 17% need Renal Replacement Therapy (RRT).[19] Moreover, postoperative AKI results in a high mortality, which has been linked to the serum creatinine (S. Cr) peak[20] the need for postoperative dialysis.[20] The duration of RRT and the presence of other comorbidities such as sepsis, encephalopathy and coagulopathy.[21]

Avoiding prolonged cold or warm ischaemia time of transplantation could also reduce organ injury from reperfusion.

CONCLUSION

In this preliminary observation, there is a progressive rise in creatinine among patients who had a baseline creatinine of >1.2 mg/dL.

A higher MELD score did not correlate with postop AKI even though the MELD score is heavily weighted by creatinine levels.

It is possible that even though many of these patients were believed to have HRS, underlying renal disease due to glomerulopathies or due to comorbidities may exist.

Thus, as far as possible, any patient with renal dysfunction in the presence of CLD being planned for a liver transplant should have a renal biopsy when technically possible.

Selection of patients for CKLT should be based on strict guidelines and establishment of preop diagnosis of CKD.

There are as yet no definitive guidelines regarding the selection of patients for CKLT. Thus, establishment of moderate or severe interstitial fibrosis and tubular atrophy would help take a more scientific decision regarding CKLT.

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