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CLINICAL CHARACTERISTICS AND CORRELATION WITH DEGREE OF LIVER STIFFNESS IN POST LIVER TRANSPLANT PATIENTS IN A TERTIARY CENTER IN SOUTH INDIA.

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ABSTRACT **Background:** Post liver transplant steatosis remains a common complication and its early detection by liver biopsy remains a challenge for the transplant physician due to invasive and expertise of the procedure. Transient elastography has shown promise in some recent studies as noninvasive alternative in transplant recipients. **Methods:** We conducted a prospective cross-sectional study over 6 months, in liver transplant recipients who were at 1 year post transplantation to assess the correlation of peri-transplant factors to transient elastography values. A total of 49 patients were screened of which 38 were recruited. Transient Elastography was performed in all the patients using Fibroscan 430 mini + ®. An examination was considered invalid if IQR > 30. Statistical analysis was done using SPSS® software. Pearsons and Spearman correlation were used to determine association. **Results:** In our analysis, we found no significant correlation between donor age, graft weight and recipient age with controlled attenuation parameter (r=0.18 p=0.284; r=0.07 p=0.697; r=0.21p=0.198 respectively). Etiology of the primary liver disease did not show any significant correlation with post-transplant steatosis (r=7.385, p=0.689). However, a significant moderate correlation between serum ALP values was observed with CAP measurements (r=0.36, p=0.026). **Conclusion:** Our study aims to explore the utility of peri-transplant factors combined with transient elastography as a noninvasive tool in assessing early post-transplant graft dysfunction. From our analysis we could draw correlation between serum alkaline phosphatase and CAP values which reflect the steatosis in graft. Combination of biochemical parameters and transient elastography can be used in future for noninvasive and more robust prediction of early graft dysfunction, without the need for biopsy. According to our knowledge, this is the only study done in Indian population for such patient population and can be used as a pilot for future studies.

KEYWORDS : Transient Elastography, Controlled attenuation parameter, Graft steatosis, Graft fibrosis, Post Liver Transplantation.

INTRODUCTION:

Liver transplantation is a curative treatment for patients with end stage liver diseases (1), with improved outcomes due to the advent of modern immunosuppressive regimens and improvements in surgical techniques. However, liver steatosis is a common complication in post liver transplant patients and it has been estimated that one in every third of liver transplant recipients for non- NASH indication develops steatosis on long term. (2)

30% recurrence of fibrosis is an also a universal recurrence following transplantation in patients with hepatitis C who underwent transplantation on 5 years follow up. (3–5). Hence it is implicit for transplant physician to monitor the LT patients closely and intervene at an early stage to prevent cirrhosis and subsequent re- transplantation.

Liver biopsy is the gold standard for diagnosing graft fibrosis, but it is not an ideal tool for serial monitoring being an invasive test with risk of complication, requiring technical expertise, cost and a propensity for sampling errors. (7,8) necessitating to use of non- invasive markers as a screening modality.

Fibroscan® as a non-invasive tool has been studied to assess liver stiffness in non-transplant population. (9,10) but research on its utility in post-transplant population are relatively sparse. Also, the findings from normal population cannot be extrapolated in LT population, primarily due to significant changes to anatomy, prevalence of metabolic syndrome and its components. (13,14). Transient elastography has shown to play promising role in identifying hepatic steatosis and fibrosis in post-transplant patients like liver biopsy. (11,12). Hence this study is undertaken to determine the correlation of peri transplant factors with post-transplant steatosis using non-invasive method as a primary tool.

MATERIAL & METHODS:

Inclusion criteria: All post-transplant patients who were on follow-up at Government Stanley Hospital, Chennai; and were of age 14 years or more with at least 1 year post transplantation, at the commencement of the study were enrolled. The study was prospectively done for 6 months.

Exclusion criteria: Patients less than 1 year post transplantation, with acute or chronic rejection, cholestasis or hepatitis, concurrent heart failure, implantable cardiac devices were excluded from the study. VCTE was performed for all the patients, and additionally ultrasonographic evaluation was done. The study was approved by the institution ethics committee (vide EC/NEW/INST/2020/461) and all the patients were subjected to voluntary consent before inclusion.

METHODOLOGY

Vibration controlled Transient Elastography was done for all the enrolled patients using Fibroscan® Mini 430 +. Experienced single operator, who was unaware of the clinical details performed the procedure using standard protocol, after overnight fasting in the subjects. Procedure was done in supine position with the right arm in maximal abduction and measurements were taken over the right hepatic lobe through the intercostal space. (15) Standard M probe was used for all the patients with normal BMI, while XL probe was used for Obese patients. LSM and CAP values were noted simultaneously. Mean of 10 valid measurements were taken. Median/IQR > 30 was considered as invalid. Data was collected and analyzed using SPSS® software. Pearsons and Spearman correlation were used for determining association. Kruskal Wallis test was used for subgroup analysis.

RESULTS

Out of 49 total patients screened, 38 were included in the study. Patient characteristics are listed in (Table 1). The study cohort comprised individuals with a mean age of 37.16 years, and a majority of whom were males (76.3%). The primary etiology for liver transplantation was Ethanol-related cirrhosis (26.3 %), followed by Wilson's disease (21.1 %). The mean duration of post- transplant period was 4.42 years.

The donor characteristics are listed in Table 2. Most of the donors in our study population were deceased (76.3%), with a mean donor age of 28.16 years and mean graft weight of 865.92 gm. The mean BMI (Kg/m^2) of participants on enrollment was 25.65. Mean Hemoglobin and platelet counts were 11.43 g/dL and 186.47 $x10^3/mm^3$ respectively. Serum creatinine levels were 1.08 mg/dL. Other investigations are listed in Table 3.

Table 1: Patient Characteristics:

Patient Characteristics	Mean ± SD	Median (IQR)	Min-Max OR N (%)
Age (Years)	37.16 ± 17.25	40.50 (19.00-54.00)	14.00 - 62.00
Age			
<20 Years			11 (28.9%)
20-29 Years			5 (13.2%)
30-39 Years			3 (7.9%)
40-49 Years			6 (15.8%)
50-59 Years			11 (28.9%)
60-69 Years			2 (5.3%)
Gender			
Male			29 (76.3%)
Female			9 (23.7%)
Duration Post Transplant (Years)	4.42 ± 3.87	4.00 (1.00-5.75)	1.00 - 18.00
Primary Indication Of LT			
Ethanol Related			10 (26.3%)
Wilsons Disease			8 (21.1%)
Cryptogenic			7 (18.4%)
HBV			3 (7.9%)
NASH			3 (7.9%)
PFIC			2 (5.3%)
Acute Liver Failure			1 (2.6%)
Budd Chiari Syndrome			1 (2.6%)
Carolis Disease			1 (2.6%)
Cholesterol Ester Storage Disease			1 (2.6%)
Congenital Biliary Atresia			1 (2.6%)
MELD At Transplantation	19.18 ± 4.76	19.00 (17.00-21.00)	8.00 - 30.00
Procedure Characteristics			
Whole Liver Transplantation			29 (76.3%)
Left Lobe			9 (23.7%)
Duration Of Surgery (Hours)	9.61 ± 1.78	10.00 (8.25-10.00)	6.00 - 14.00

We observed a median (IQR) LSM score of 6.80 (5.6-7.77) Kpa and a mean CAP score of 274.79 dB/m. Considering the cutoff score of 270db/m for detection of any steatosis and cutoff score of 7.4 kPa for detection of any grade of fibrosis;(15) only 34.8 % had evidence of steatosis while 42.1% had some degree of fibrosis. 50.0% (n=19) of participants had a normal liver echotexture on routine sonography, while 39.5% (n=15) and 10.5% (n=4) had Grade 1 and Grade 2 fatty liver respectively.

Table 2: Donor Characteristics:

Donor and Reciepient Details	Mean ± SD	Median (IQR)	Min-Max OR N (%)
Donor Age (Years)	28.16 ± 8.92		
Donor Type			
Deceased			29 (76.3%)
Living			9 (23.7%)
Donor Gender			
Male			27 (71.1%)
Female			11 (28.9%)
Graft Weight (g)		949.00 (481.75-1130.00)	
Reciepient Age (Years)		36.50 (16.50-47.75)	
Reciepient Blood Group			
B+ve			12 (31.6%)
A+ve			9 (23.7%)
O+ve			9 (23.7%)
AB+ve			6 (15.8%)
B-ve			1 (2.6%)
O-ve			1 (2.6%)

On correlation analysis, we observed that post- transplant duration, duration of surgery, graft weight and age of patient at time of transplantation did not show any significant correlation with graft stiffness or steatosis values (Table 4). A moderately significant correlation was found between ALP and CAP values (r=0.36, p=0.026) (Figure 1).

Also, a strong positive and significant correlation was observed between CAP and LSM values (r=0.77, p<0.001) (Figure 2). Serum levels of tacrolimus did not have any significant correlation with the post-transplant steatosis in our observation.

Table 3: Correlation with various parameters.

Parameters	Correlation coefficient (LSM)	P	Correlation coefficient (CAP)	P value
Duration Post Transplant (Years)	-0.09	0.589	0	0.993
MELD At Transplantation	-0.21	0.215	-0.23	0.196
Duration Of Surgery (Hours)	-0.1	0.556	0.07	0.659
CIT (Minutes)	-0.27	0.105	-0.2	0.222
WIT (Minutes)	0.05	0.616	0.07	0.665
Donor Age (Years)	0.23	0.165	0.18	0.284
Graft Weight (g)	0.05	0.629	0.07	0.667
Reciplent Age (Years)	0.11	0.520	0.21	0.198
Current BMI (Kg/m²)	-0.06	0.706	0.12	0.464
Hemoglobin (g/dL)	-0.23	0.159	-0.07	0.666
Platelet Count (x10³/mm³)	0.06	0.710	0.12	0.464
ALP (U/L)	0.19	0.253	0.36	0.026
Total Protein (g/dL)	0.31	0.062	0.31	0.058
S. Albumin (g/dL)	0.22	0.192	0.33	0.040
Serum Tacrolimus Levels	0.2	0.229	0.26	0.121

DISCUSSION:

Evaluation and management of post-transplant graft steatosis and fibrosis remain a significant challenge for the transplant physicians. Through our study we tried to evaluate the association of LSM and CAP with peri-transplant patient factors. Fibroscan has not been studied well in post- transplant population and there is a lack of large-scale data. *Chayanupatkul et al* in their study of 150 post transplantation patients, had observed that out of 5 patients who developed chronic allograft rejection, 3 had moderately significant raised ALP values.

They had also observed that 34 patients had severe steatosis by TE despite having normal transaminase levels; which suggests that even normal transaminase levels can have detectable fibrosis via TE in this patient population. Further, they had argued that the elevations of ALP found in chronic graft rejection patients could be due to post transplant cholestasis, which could have influenced LSM values. (16) In our study have found a positive significant correlation of graft steatosis with ALP values. Although, arguments put forward by *Chayanupatkul et al* seem to be valid, it must be noted that available data suggests that ALP levels up to 10 times or more can have a significant impact on LSM values. (17) Based on these findings we suggest that serum ALP along with CAP values may be evaluated as an early indicator of graft steatosis and dysfunction. Also patients with normal transaminases should be included for screening transient elastography, especially if high clinical suspicion of metabolic syndrome or graft dysfunction is there clinically.

Finding of a strong positive correlation between steatosis and fibrosis values indicated by CAP and LSM respectively, is also noteworthy. A similar observation was made by *T. karlas et al* in their study of 204 patients had compared the pretransplant characteristics with TE parameters and had noted that an increased LSM > 7.9 Kpa was associated with a higher steatosis value in the graft. (18)

Since post- transplant NASH is fairly common but often underdiagnosed and poorly characterized (19), the positive association of post-transplant CAP with LSM may help to identify high risk individuals and serve as an early predictor for subsequent cirrhosis in such patients.

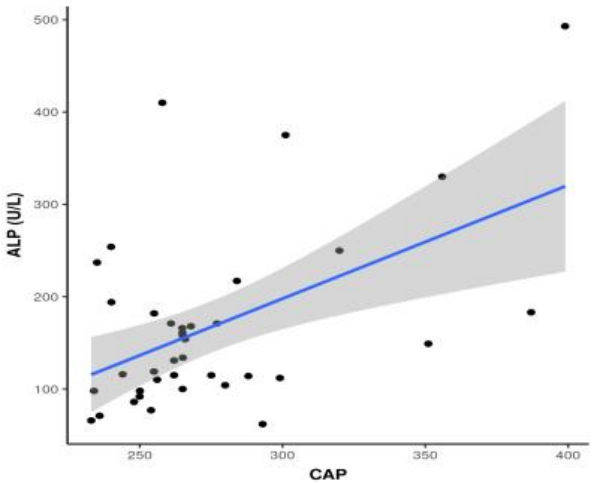

Figure 1: Correlation of ALP and CAP

A similar study to ours was done by *Ivana et al* on 175 participants, and they had observed that male gender, older age and patients with pretransplant alcoholic liver disease had higher grade of steatosis and fibrosis post LT by TE.(20) However in contrast, our study population had a higher steatosis value in patients who had pretransplant liver disease due to HBV and NASH, but there was no significant difference between etiological groups in terms of LSM (Kpa) ($\chi2 = 10.792$, $p = 0.374$) and CAP measurements ($\chi2 = 7.385$, $p = 0.689$). Immunosuppression is known to cause metabolic dysfunction post transplantation. CNIs in particular cause this affect via variety of mechanisms (21). Although CNIs are known to cause metabolic dysfunction in post- transplant recipients, evidence is conflicting regarding the role of tacrolimus- based regimes in post-transplant graft steatosis (22–24). In our analysis we found no significant correlation between serum tacrolimus levels and TE measurements, suggesting its less important role in diagnosing early graft steatosis. ($r=0.2$ $p=0.229$; $r=0.26$ $p=0.121$).

LIMITATIONS:

We acknowledge the limitations that have affected our study. The most obvious is the lack of liver biopsy to confirm our findings on histopathology. This was due to the lack of confidence among participants to undergo an invasive procedure post-transplant. Also the smaller sample size limited our evaluation for regression analysis.

CONCLUSION:

According to our knowledge, this is the only study from India done on non-invasive methods and correlation with clinical findings in Post transplant recipients. Findings of positive correlations of ALP and LSM with CAP values, similarly reported by other authors highlight the importance of exploring multimodal non-invasive methods that include both biochemical and radiological in early evaluation of graft dysfunction. We suggest that TE can be considered as a screening modality for allograft steatosis and fibrosis even when liver chemistries are normal. Scoring systems and prognostic models based on both fibroscan and biochemical investigations can be developed, and validated in future studies.

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