Prevalence of Renal Dysfunction Among Pediatric Liver Transplant Recipients

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Introduction. Renal dysfunction is among the common and considerable complications after liver transplantation and is principally attributable to immunosuppressive medications .The purpose of this study was to define the prevalence of hypertension and renal dysfunction among pediatric liver transplant recipients.
Methods. 46 pediatric liver transplant recipients were assessed for hypertension utilizing ambulatory blood pressure monitoring (ABPM), and glomerular, and tubular renal function at the transplant clinic of Shiraz University of Medical Sciences. Results were analyzed using SPSS 19 and *P* value < .05 was considered statistically significant.
Results. The mean age of the patients was 12.2 ± 3.3 years and 24 of them were female. Considering ABPM measurements 20 patients (43.5%) were hypertensive, 37% were systolic and 36.6% were diastolic non-dippers respectively. eGFR was calculated based on different formulations and Cystatin C–based equation estimated lower GFR than Cr-based equation. Micro-albuminuria was noticed in 26.1%. Additional parameters of tubular dysfunction included hyperuricosuria (4.3%), hypercalciuria (6.5%), abnormal fractional excretion of Mg (FeMg) (43.5%), abnormal tubular reabsorption of phosphate (TRP) (4.3%), and abnormal fractional excretion of uric acid (FEUA) in 13% of the patients. We noticed a statistically significant negative correlation between hypercalciuria, microalbuminuria, FeMg (*P* < .05) and GFR.
Conclusion. Renal function impairment and hypertension are frequent complications amongst pediatric liver transplant recipients. Using Cyctatin C instead of Cr based formula for GFR estimation, and blood pressure monitoring by ABPM and regular screening of renal function are essential measures for recognition and treatment of renal dysfunction in these patients.

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INTRODUCTION

Liver transplantation (LT) is considered to be the preferred cure alternative for children with end stage liver disease. In recent years, survival rate after LT has improved, and the current 5-year living and deceased graft survivals are 92% and 85% respectively.[1]

Because of improved life expectancy, long- term extra-hepatic complication after LT has become a major concern.[2,3] Impaired kidney function with multi-factorial background is one of the well-recognized long-term complications after non-

renal solid organ transplantation.[4-7] As rejection rates are improving after pediatric solid organ transplantation, much of the focus is shifting toward the prevention of collateral organ damage, such as nephrotoxicity.[8]

The main determinant of post-transplant renal dysfunction is thought to be pre-transplant renal function. Emerging renal function impairment after liver transplantation is thought to be multifactorial[9] but the most defined etiology is thought to be the nephrotoxicity of calcineurin inhibitors, which are the keystone of anti-rejection regimens.[10] Other potential causes of renal impairment in these patients include hypertension (HTN) and proteinuria.[11,12]

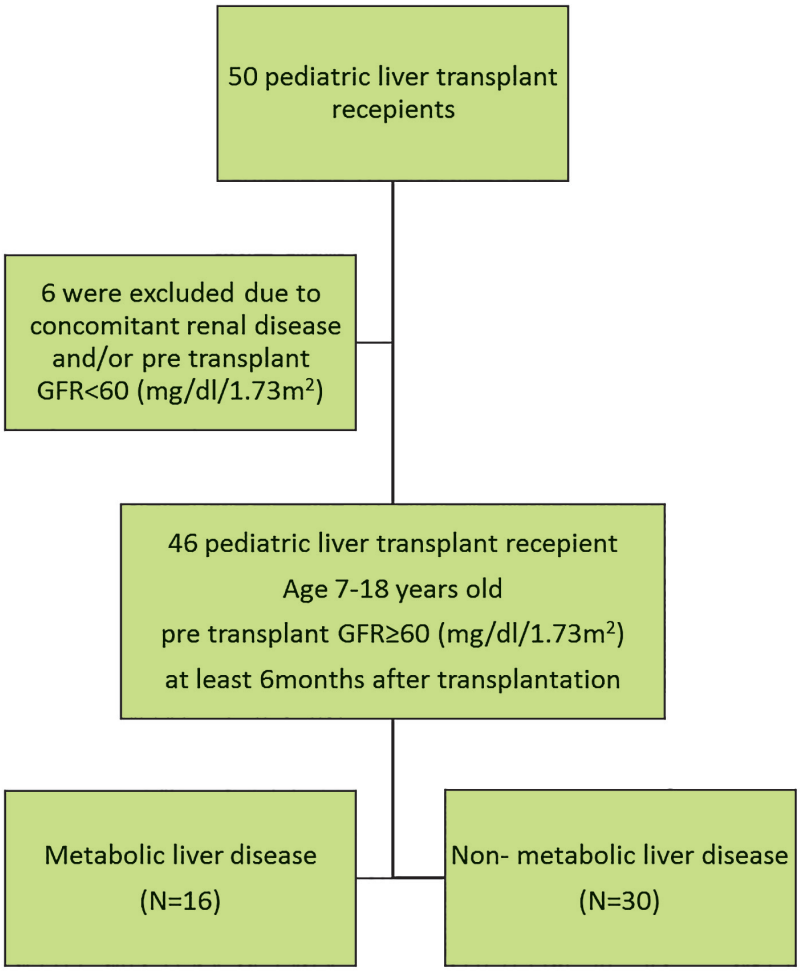
Arterial HTN is one of the most prevalent complications in LT recipients.[11] Proteinuria is correspondingly common and is predominantly consequence of calcineurin induced nephrotoxicity. Another risk factor for chronic kidney disease (CKD) is microalbuminuria that denotes presence of albumin above normal ranges in urine but not as high as to be detected by routine laboratory methods.[12]

The aim of this study was to determine the prevalence of HTN and renal dysfunction in pediatric liver transplant recipients.

MATERIALS AND METHODS

Setting and Sampling

The study was conducted during one year from 2015 to 2016 and 50 pediatric liver transplant recipients who had regular follow-up visits at the transplant clinic of Shiraz University of Medical Sciences were enrolled in this study. 46 patients who full filled the inclusion criteria (age ranged from 7 to 18 years, at least 6 months post-transplant duration, and pre transplant GFR ≥ 60 mL/min/ 1.73m^2) were eligible and those with concomitant known renal disease and GFR < 60 mL/min/ 1.73m^2 were excluded (Figure). Local



It shows flowchart of our study population with the patient inclusion and exclusion criteria.

ethics committee approved the study. Informed consent was obtained from the patients and parents. Patients data including demographics, post-transplant duration, antihypertensive drug, serum and urine creatinine (Cr), calcium (Ca), uric acid (UA), magnesium (Mg), and phosphate (Ph), serum cystatin C, tacrolimus level (by nephlometry method), urinary microalbumine were collected and fractional excretion of Mg (FeMg), fractional excretion of UA (FeUA), and fractional tubular reabsorption of Phosphorous (TRP) were calculated. Microalbuminuia was defined as spot urine microalbumin/Cr > 30. FeMg was calculated as; (Urine Mg × plasma Cr) / (0.7 × plasma Mg × urine Cr) × 100. Values above 4% were considered abnormal. Hyperuricosuria was defined as urinary uric acid excretion above 0.53 mg/dL GFR and was calculated as urine UA × serum Cr/ urine Cr × serum UA). FeUA above 15% was considered abnormal in current study. Hypercalciuria was defined as spot urine Ca/Cr value above 0.2.

TRP which is the fraction of Phosphorous (Ph) in the glomerular filtrate that is reabsorbed in the renal tubules was defined as: 1: (serum Cr × urine Ph / urine Cr × serum Ph) × 100. TRP values less than 80% was considered abnormal.

Glomerular Filtration Rate (GFR)

GFR was calculated according to Cr and Cystatin C-based equations using four methods as follows; the Schwartz formula: K × height $_{(cm)}$ / serum Cr $_{(mg/dL)}$, the KDIGO formula: 70.6 × (cystatin $C^{-0.931}$), the Filler's formula: Log (GFR) = 1.962 + [1.123 × log (1/cystatin $C_{mg/dL}$) and Creatinine-Cystatin C-Based CKID Equation: eGFR = 39.8 x $[ht/Scr]^{0.456}$ × $[1.8/cysC]^{0.418}$ × $[30/BUN]^{0.079}$ × [1.076male] [1.00 female] × $[Ht/1.4]^{0.179}$.

Blood Pressure (BP)

Office BP was measured via auscultation method with a mercury sphygmomanometer (three records after 5 min rest in a sitting position from the arm with no fistula using an appropriately sized cuff) on the day of ambulatory BP monitoring (ABPM). To compensate for differences in age and body size, the BP records were indexed by dividing the measured value into age, sex, and height -specific 95th BP percentile. The subjects were considered hypertensive when the indexed BP was more than > 1.0.[13] The ABPM was performed with Suntech Oscar II (Morrisville, NC, USA). The device was set to take the measurements every 20 minutes during the day and every 30 minutes during sleep. The patients or parents were told to keep a diary to record events round the clock, including the awake and asleep times. ABPM (24–h systolic and diastolic, day-time, and night-time) were compared with the European norm[14] and indexed by dividing each value by gender and height specific 95th BP percentile. Blood pressure index (BPI) ≥ 1 was described as systolic and or diastolic values more than 95th percentile for gender and height. HTN was defined as daytime and/or nighttime systolic and or diastolic BP ≥ 95th percentile for healthy children or the use of antihypertensive medications. Dipping was defined at least 10% BP decline during the night and calculated as (mean day time – mean night time / mean day time) × 100.

Chronic Kidney Disease (CKD)

According to National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guideline, CKD staging is defined as; Stage I) Kidney damage with normal or increased GFR > 90 mL/min/ 1.73m^2, Stage II) GFR 60–89 mL/min/ 1.73m^2, Stage IIIA) GFR 45 to 59 mL/min/ 1.73m^2, Stage IIIB) GFR 30 to 44 mL/min/ 1.73m^2, Stage IV) GFR 15 to 29 mL/min/ 1.73m^2, and Stage V) GFR < 15 mL/min/ 1.73m^2 or dialysis.

Statistical Analysis

Data were presented by the median, mean, and standard deviation for continues variables or number and percentage for categorical variables then were analyzed by Chi-square, Student t-test, and intra-class correlation coefficient utilizing SPSS 19 (IL. Chicago. USA) and MEDCALC and *P* value < .05 was considered statistically significant

RESULTS

Patients

Forty-six pediatric liver transplant recipients (22 male (47.8%) and 24 female (52.2%)0 aged 7 to 18 years (12.2 ± 3.3 years) were enrolled in this study. All the patients were under treatment with tacrolimus and no one was taking antihypertensive medications. The patients' characteristics including their underlying primary liver diseases distribution are shown in Table 1. Primary liver disease of the

Table 1. The Patients' Characteristics and Renal Function Parameters

Variable	Mean ± SD / Number (%)	Range
Age, years	12.2 ± 3.3	7 to 18
Gender (male), n (%)	22 (47.8%)	
Height, cm	145.1 ± 16.4	102 to 180
Post-transplantation Duration, month-year	29.8 ± 26.1	6 mo to 13 y
GFR, mL/min/ 1.73m^2		
Schwartz Formula	149.5 ± 36.2	51 to 281
Fillers Formula	85.6 ± 21	39 to 151
KDIGO Formula	66.4 ± 14.4	37.5 to 110
CKID Formula	81.8 ± 13.23	38 to 119
Cystatin C, mg/dL	1.12 ± 0.26	0.62 to 1.97
Tacrolimus Trough Level, ng/mL	10.9 ± 5.3	2.6 to 28
Liver disease, n (%)		
Metabolic Disease	16 (34.8)	
Wilson Disease	13 (81.3)	
Tyrosinemia	3 (18.7)	
Nonmetabolic Disease	30 (65.2)	
Autoimmune Hepatitis	6 (20)	
Cryptogenic Cirrhosis	9 (30)	
Hypercholesterolemia	6 (20)	
Neonatal Hepatitis	4 (13.3)	
PFIC	2 (6.7)	
Crrigler Najjar	2 (6.7)	
Billiary Atresia	1 (3.3)	
Serum BUN, mg/dL	14.04 ± 4.29	8 to 29
Serum Cr, mg/dL	0.6 ± 0.18	0.4 to 1.4
Serum Ca (Nl: 8.5 - 10.5)	9.2 ± 0.65	7 to 10.3
Serum Uric Acid, mg/dL	3.4 ± 1.5	1.3 to 8.8
Serum P	4.83 ± 1.51	3.6 to 6.3
Serum Mg	1.69 ± 0.28	1.1 to 2.5
Microalbuminuia (Urine Microalbumin/Cr > 30)	12 (26.1%)	
Hyperuricosuria (> 0.53 GFR)	2 (4.3%)	
Hypercalciuria (Urine Ca/Cr > 0.2)	3 (6.5%)	
TRP < 80%	2 (4.3%)	
FEMg > 4%	20 (43.5%)	
FEUA > 15%	6 (13.0%)	

SD, standard deviation; GFR, glomerular filtration rate; PFIC, progressive familial intrahepatic cholestasis; FEMg, fractional excretion of magnesium; FEUA, fractional excretion of uric acid; TRP, fractional tubular reabsorption of phosphorous
Microalbuminuria classified as mixed glomerular and tubular function.

recipients was categorized as metabolic and non-metabolic disease.

Tubular and Glomerular Function Assessment

As seen in Table 1 microalbuminuria, hyperuricosuria and hypercalciuria were observed in 26.1%, 4.3%, and 6.5% of patients; respectively. There was a statistically significant correlation between post transplantation duration and hypercalciuria ($P < .05$) and FEMg ($P < .05$). There was no correlation between post transplantation duration and other tubular parameters and tacrolimus level ($P > .05$). GFR was estimated via four formulations that are presented in Table 1. Intraclass Correlation Coefficient (ICC) was used to compare different methods of GFR estimation. Based on the 95% confident interval of the ICC estimate, values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability; respectively.[14] ICC of average measures for all four methods of GFR calculations was 0.31 (CI: 0.17 - 0.48) which indicated a poor reliability . There was also a poor reliability between Schwartz's and Filler's formula, ICC: 0.16 (CI: -0.51 - 0.53) and KDIGO and Schwartz's formula

ICC: 0.11 (CI: -0.6 - 0.5) but there was a strong reliability between two cystatin c-based equations (Fillers and KDIGO) ICC: 0.95 (CI: 0.92 - 0.97). The CKID formula which is based on both creatinine and cystatin C also has moderate reliability with Schwartz's formula (ICC:0.53, CI: 0.16 - 0.74) and good reliability with KDIGO and Fillers equations (ICC: 0.82,CI: 0.68 - 0.9; and ICC:0.78, CI: 0.6 - 0.88; respectively).

Table 2 presented the CKD stages considering different methods of GFR estimation. According to KDIGO formula 33% of patients (15 cases) were in stage III CKD that was in contrast with other methods of estimation (4.3%, 2.2%, and 2% according to Filler's, Schwartz's and CKID formula; respectively). There was no correlation between GFR and tacrolimus serum level, post transplantation duration, CKD staging and underlying liver disease ($P > .05$).

Table 3 shows the comparison of some variables (GFR, TRP, FEMg, FEUA, Ca/Cr, and Albumin/Cr) according to the primary liver disease (metabolic versus non metabolic liver disease). As the table demonstrates although all variables were higher in metabolic comparing to non-metabolic group ($P > .05$) only urinary Ca/Cr ratio was significantly different between mentioned categories (0.1 ± 0.01 vs. 0.05 ± 0.04, $P < .05$). Twelve patients (26.1%) had microalbuminuria. There was a significant correlation between post-transplant duration and microalbuminuria ($P < .05$).

Blood Pressure Evaluation

As demonstrated in Table 4, office measurement showed 7 patients (15.2%) with high BP that 2 of them were normotensive according to ABPM measurements. ABPM identified 20 patients with high BP (43.5%). which only 5 of them was hypertensive according to office measurements. According to the above results 67.3% of our patients had masked hypertension and 15.2% had true hypertension. None of our patients had white coat phenomena. Nine hypertensive patients (45.0%) according to ABPM had both day and nighttime HTN, also 2 (10.0%) and 9 (45.0%) patients had isolated daytime and nighttime HTN; respectively. Systolic none dipping was identified in 17 (37%) patients and diastolic non-dipping in 15 (32.6%). There was no correlation between HTN and tubular function, GFR and post transplantation duration ($P > .05$).

Table 2. CKD Classification According to Estimated GFR Based on 4 Different Equations

CKD Classification	Schwartz Formula	Fillers Formula	KDIGO Formula	CKID Formula
Grade 1, ≥ 90mL/min/ 1.73m^2	45 (97.8%)	13 (28.3%)	2 (4.3%)	12 (26%)
Grade 2, 60 to 89 mL/min/ 1.73m^2	0	31 (67.4%)	29 (63%)	32 (69%)
Grade 3				
A (45-59ml/min/1.73m^2)	1 (2.2%)	2 (4.3%)	13 (28.4%)	1 (2%)
B (30-44ml/min/1.73m^2)	0	0	2 (4.3%)	1 (2%)
Grade 4, 15 to 29 mL/min/ 1.73m^2	0	0	0	0
Grade 5, < 15 mL/min/ 1.73m^2	0	0	0	0

CKD, chronic kidney disease; GFR, glomerular filtration rate.

Table 3. Comparison of Some Renal Variables and Underlying Liver Diseases Group

Variable	Mean ± Standard Deviation		*P*
	Metabolic Disease	Non Metabolic Disease	
GRF, mL/min/ 1.73m^2			
Schwartz Formula	152.2 ± 42.3	148.2 ± 33.2	> .05
Fillers Formula	66.4 ± 16.1	64.9 ± 13.5	> .05
KDIGO Formula	88.9 ± 23.5	83.9 ± 19.7	> .05
CKID Formula	84.43 ± 13.83	80.4 ± 12.9	> .05
TRP, NI: < 80%	92.2 ± 0.04	92.4 ± 0.05	> .05
FEMg, NL < 4%	4.4 ± 3.5	3.8 ± 2.3	> .05
FEUA, NI < 15%	11.7 ± 6.5	7.2 ± 4.0	> .05
Microalbumin / Cr (NI < 30), mg/g	26.8 ± 18.5	20.3 ± 20.1	> .05
Calcium/ Cr (NL < 0.2), mg/mg	0.1 ± 0.01	0.05 ± 0.04	< .05

GFR, glomerular filtration rate; FEMg, fractional excretion of magnesium; FEUA, fractional excretion of uric acid; TRP, fractional tubular reabsorption of phosphorous

Table 4. The Distribution of Blood Pressure Parameters Among Total Population and Hypertensive Patients

Variables	Mean ± SD (Median)	
Blood Pressure, mmHg		
Office SBPI	0.83 ± 0.11 (0.84)	
Office DBPI	0.80 ± 0.13 (0.79)	
Day-time SBPI	0.95 ± 0.08 (0.94)	
Day-time DBPI	0.86 ± 0.08 (0.87)	
Night-time SBPI	0.96 ± 0.1 (0.96)	
Night-time DBPI	0.93 ± 0.1 (0.94)	
24-h SBPI	117.17 ± 10.5	
24-h DBPI	1.0 ± 0.09	
Systolic Dipping (n, %)	29 (63.0%)	
Diastolic Dipping (n, %)	15 (32.6%)	
Masked HTN (n, %)	31 (67.3%)	
True HTN (n, %)	7 (15.2%)	
Normotensive (n, %)	8 (17.3%)	
WCH (n, %)	0 (0%)	
Hypertensive Patients	**Number (Percent)**	
	ABPM	**Office Method**
Overall Hypertensive Patients	20 (43.5%)	7 (15.2%)
Systolic HTN	6 (30.0%)	2 (28.6%)
Diastolic HTN	2 (10.0%)	2 (28.6%)
Systolic and Diastolic HTN	12 (60.0%)	3 (42.8 %)

SD, standard deviation; ABPM, ambulatory blood pressure monitoring; SBPI, systolic BP index; DBPI, diastolic BP index; HTN, hypertension; WCH, white coat hypertension

DISCUSSION

Chronic kidney disease is among the main comorbidities that influence the life of LT recipients. Recognizing the risk factors and careful management and prevention of CKD may improve the prognosis of these patients. Generalized use of calcineurin inhibitors has been suggested to be the leading cause of chronic renal impairment in these patients.[16] Despite the lower dose of immune suppression comparing to other solid organ (heart and lung) transplantations these patients are at increased risk for CKD.[17] Previous studies publicized that renal dysfunction in these patients may lead to prolonged hospital stay, postoperative dialysis, infection, acute rejection, and reduced survival.[18,19] In a review by Matloff *et al* nearly 40% of pediatric liver transplant recipients developed CKD.[20] This was relatively similar to our result which showed CKD stage 3 in 33% of LT recipients. In another study on pediatric LT recipients, Herlenius *et al.* reported a significant reduction in GFR during the first six months post-transplantation and 18% of their patients were categorized as stage 3 CKD five years after liver transplantation.[21]

The measurement of kidney function after liver transplantation is also a clinical challenge.

In cirrhotic patients Cr and Cr base equations tend to overestimate GFR and assessing the clearance of iohexol remains the only reliable and gold standard method for estimating GFR.[22] Since this method is expensive and complex and is generally not applicable to be used in daily practice[18] and calculating GFR based on serum cystatin C could be a preferred alternative that is not influenced by age, sex, muscle mass, and is not altered by serum bilirubin, inflammation, or malignancy.[18,23,24] In our study we utilized four different methods for calculating GFR, which are applicable in daily practice. Patients could be categorized in more different CKD staged according to GFR formulas that were based on Cystatin C rather than the Schwartz's formula, which is only based on creatinine; therefore we recommend that GFR equations, which are based on serum Cystatin C, may have higher accuracy in the diagnosis of renal clearance rate.

In contrast to other studies,[25,26] we demonstrated a significant correlation between post-transplant duration and microalbuminuria, hypercalciuria, and FeMg. According to these findings we concluded that renal impairment occurs progressively over time, thus it is important to screen renal function in regular intervals especially in patients with primary metabolic liver disorder. Furthermore reducing the CNI dosage is another strategy to minimize the progression of renal impairment in these patients. Micro-albuminuria was detected in 26.1% of our patients. Proteinuria is not only a marker of kidney damage, but also is responsible for progression of kidney injury. The increase in urinary protein directly has toxic effect on glomerular capillary wall and tubular cells leading to interstitial fibrosis and glomerulosclerosis. In a study by Anastaze *et al.* proteinuria decreased steadily but insignificantly after liver transplantation in children and there was a significant positive correlation between urine Protein/Creatinine and tacrolimus level ($P < .05$).[27] Li *et al.* studied the impact of pre transplantation and new onset post-transplantation proteinuria on renal function and concluded that rate of renal dysfunction and mortality was higher in patients with persistent proteinuria.[28]

Tubular dysfunction was verified by the presence of phosphaturia and hyperuricosuria which mainly indicates the function of proximal tubules,

hypermagnesuria and hypercalciuaria, which are reliant mostly on the normal function of Henle and distal nephrons respectively.

Hypertension

Beyond the first year of transplantation cardiovascular disease is one of the most common causes of death in LT recipients and definitely untreated HTN is a main hazard for cardiovascular events and CKD progression.[27] The principal etiologies of post-transplant HTN include CNI use, stimulation of rennin release, up-regulation of angiotensin II receptor, decreased GFR, enhanced sodium reabsorption, sympathetic over activity, use of corticosteroids, and impaired vasodilation system due to reduced production of prostacyclin and nitric oxide.[12]

Most studies report HTN prevalence of 30 to 50% in the liver transplant recipients.[12,28] It has been reported that HTN was more prevalent within the first month after liver transplantation.[29] Alteration of the "normal" circadian rhythm is very frequent in liver transplant recipients and AMBP is considered the method of choice in determining HTN in this population.[30] In our study, prevalence of HTN was 43.5% according to ABPM and 15.2% by office method, and office method missed 75% of hypertensive patients and overestimated in 28.6%. Screening for HTN is improved by ABPM, which affords the ability to assess for white coat, dipping. In studied group, systolic and diastolic none dipping were 37% and 35%, correspondingly.

One limitations of this study was the cross-sectional design and for better understanding of renal dysfunction in pediatric liver transplant population long term follow up is warranted. Most of our patients were on low dose of corticosteroid therapy which may slightly influence the blood pressure in these patients. GFR in this study was calculated by four different formulas but as mentioned above estimating GFR by the means of iohexol clearance is the gold standard which is not applicable in routine clinical practice.

CONCLUSION

Renal dysfunction after liver transplantation warrants special attention because renal function is a predicting factor for CKD and mortality rate in future and surely influences the transplanted organ function. Though, it seems reasonable to substitute cystatin C for Cr in GFR calculation. Also for more accurate monitoring of blood pressure regular ABPM is mandatory. Furthermore, long term longitudinal studies are advocated for better assessment of renal function post liver transplantation.

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