VOLUME - 15, ISSUE - 05, MAY - 2026 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Microbiology

TMP/GFR: AN EARLY MARKER OF PROXIMAL RENAL TUBULAR DYSFUNCTION IN COMPENSATED CHRONIC LIVER DISEASE (CLD) PATIENTS

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ABSTRACT **Background:** Renal dysfunction is a frequent complication in patients with liver disease. Acute kidney injury has been reported in up to 19% of hospitalized cirrhotic patients, regardless of the reason for admission. Assessment of renal function using the glomerular filtration rate (GFR) based on the Modification of Diet in Renal Disease equation presents challenges in this population. Consequently, the present study aimed to facilitate early assessment of renal function by employing the TmP/GFR equation **Materials and Methods:** we conducted a prospective observational case control study between July 2023 to August 2024 to assess the strength of association of TmP/GFR as an early marker of proximal renal tubular dysfunction in compensated CLD patients. **Results:** We selected 27 CLD patients visited in gastroenterology OPD and we found that TmP/GFR was higher in CLD patients ($p<0.001$) than in healthy controls. **Conclusions:** Our study revealed significantly higher TmP/GFR in CLD patients than in healthy controls even if there is normal serum creatinine value. Therefore, TmP/GFR could be a better early marker of renal dysfunction in compensated CLD patients.

KEYWORDS : Acute Kidney Injury, Tubular Maximum Reabsorption of Phosphate/ Glomerular Filtration Rate, Chronic Liver Disease

INTRODUCTION

Renal dysfunction commonly occurs in patients of liver disease. It has been estimated that acute kidney injury occurs in up to 19% of cirrhotic patients admitted to hospital for whatever reason.[1] Assessment of renal function by using GFR based on MDRD equation is problematic in cirrhotic patients. Early assessment of renal function, we may do by using TmP/GFR equation[2]. Kidney function is conventionally defined by estimating the glomerular filtration rate (GFR) from serum creatinine; however, all creatinine-based methods are unreliable in cirrhosis due to low creatinine production, an expanded extracellular volume with ascites, and significant muscle wasting. Although newer tubular injury markers such as cystatin C, NGAL, and KIM-1 offer higher sensitivity, their routine clinical use remains limited due to high cost. Proximal tubular function is central to phosphate handling, as about 80% of filtered phosphate is reabsorbed in the proximal tubule via Na–phosphate cotransporters (primarily NPT2a), and this process is dynamically regulated by dietary phosphate, PTH, glucocorticoids, phosphatonins (e.g., FGF-23), acid–base status, and oestrogen through modulation of transporter expression and activity.[3] The ratio of tubular maximum reabsorption of phosphate to GFR (TmP/GFR) provides an integrated, GFR-adjusted measure of proximal tubular reabsorptive capacity and may detect tubular dysfunction even when global GFR is preserved.[4] Proximal renal tubular dysfunction (PRTD) in chronic liver disease (CLD) remains under-recognised and insufficiently studied despite its potential clinical importance. Therefore, the objective of this study is to evaluate the strength of association between TmP/GFR and proximal renal tubular dysfunction as an early marker of renal dysfunction in patients with chronic liver disease.

MATERIAL AND METHODS

This was a Prospective observational case control study of compensated CLD patients, where cases included patients (both male & female) over 18yrs of age attending gastroenterology OPD between July 2023 to August 2024 of SRN hospital of Motilal Nehru Medical college Prayagraj. Ethical approval was obtained from INSTITUTIONAL ETHICS COMMITTEE MLN MEDICAL COLLEGE (Reg no: ECR/922/inst/UP/RR-22)

We excluded known case of CKD, Diabetic kidney disease, hypertension, Obstructive uropathy, UTI, Nephrotic syndrome, Congenital renal disease and hepatorenal syndrome(HRS).

Total 130 patients' data were collected. Baseline data included age, gender, and comorbidities. Symptoms and indications of OPD visit were recorded. Laboratory parameters on the OPD visit were included. Compensated CLD patients were selected on the basis of LFT, USG whole abdomen, Fibroscan and endoscopy findings. Their blood pressure, KFT, eGFR and LFT were noted.

130 healthy age and sex matched controls were selected from the general population, and similar clinical and laboratory tests were done on them.

The calculation of TmP/GFR was done after overnight fasting spot urine sample for urine creatinine and phosphorus, blood sample for serum creatinine and phosphorus was collected.

FeP = Sr.Cr × Up/SrP × Ucr (FeP = fractional excretion of phosphorus)
TRP = 1-FeP (TRP = FRACTIONAL REABSORPTION OF PHOSPHORUS)
If TRP < 0.86 then TmP/GFR = TRP × SrP
If TRP > 0.86 then TmP/GFR = 0.3 × TRP/1-(0.8TRP) × SrP[5]

Investigations include: CBC, LFT, KFT, Serum Electrolyte, blood sugar, HbA1c, Lipid profile, Serum total calcium, Urine routine microscopy, Urine micral, Urine Creatinine, Urine Phosphorus, USG whole abdomen with renal size and echogenicity, Fibroscan, Chest X Ray (PA View), ECG, Endoscopy.

The statistical analysis was performed using SPSS version 21.0. Data were presented as mean (standard deviation) for continuous variables and as percentages for categorical variables. The chi-square test was used to compare categorical variables, while the independent t-test was employed to assess differences in continuous variables between groups. Correlation analysis was conducted using Pearson's correlation coefficient (or Spearman's correlation coefficient for non-normally distributed data) to evaluate the strength and direction of the relationship between continuous variables. Regression analysis, including simple and multiple linear regression, was performed to model the relationship between dependent and independent variables. A p-value of 0.05 was considered statistically significant.

RESULTS

The mean age was 39.62± 15.71 years in case and 38.31±8.51 years in control. The mean was not significantly different between case and control. In the Case group, 73.08% were male and 26.92% were female, while in the Control group, 61.54% were male and 38.46% were female. On the basis of gender, both groups were comparable. The most common clinical complain in the cases were fatigue and jaundice.

Table 1 & Figure 1 shows the association of TmP/GFR between case and control. The Case group demonstrated significantly higher TmP/GFR levels (3.46 ± 0.79) compared to Controls (2.50 ± 0.52) (t = 5.13, p <0.001), indicating altered renal tubular function in CLD.

Table 1: Association of TmP/GFR Between Case and Control

	Case (n=130)		Control (n=130)		t	p-Value
	Mean	±SD	Mean	±SD		
TmP/GFR	3.46	0.79	2.50	0.52	5.13	<0.001

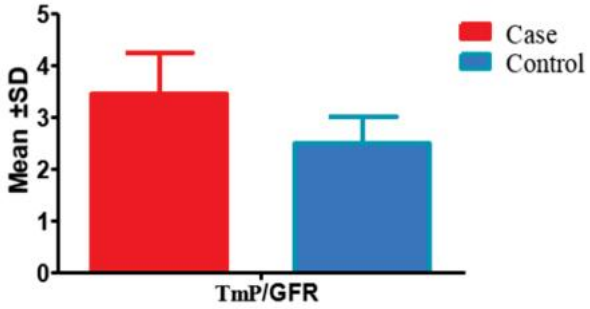

Figure 1: Shows the Association of TmP/GFR Between Case and Control.

Table 2 shows the Pearson correlations between TmP/GFR are as follows: Hb (Haemoglobin) has a moderate negative correlation of -0.45 (p = 0.021), indicating a statistically significant inverse relationship. TLC (Total Leukocyte Count) exhibits a strong positive correlation of 0.72 (p = 0.000), showing a significant positive relationship. Platelet count has a moderate positive correlation of 0.41 (p = 0.036), also statistically significant. the correlation between TmP/GFR and S.K+ is statistically significant (r = 0.41, p = 0.040), indicating a moderate positive relationship and S.Na (r = -0.15, p = 0.462) are not statistically significant. Sr. urea is statistically significant (r = 0.63, p = 0.001), indicating a strong positive relationship, meaning higher Sr. urea levels are associated with higher TmP/GFR values and Sr. creatinine is weak and not statistically significant (r = 0.11, p = 0.584), suggesting no meaningful relationship between Sr. creatinine levels and TmP/GFR. Table 3 shows the Pearson correlation of Bilirubin Total 0.53(p = 0.005), Bilirubin Indirect 0.53(p = 0.005),Bilirubin Direct 0.53(p = 0.005) indicating significant positive relationships. SGOT 0.32(P = 0.108), SGPT 0.41(P = 0.038) and Sr. albumin -0.59(p = 0.001).This suggests that while SGPT is positively associated with TmP/GFR, higher S. Albumin levels are negatively associated with TmP/GFR. SGOT does not have a significant impact. Associations of mean LFT, mean biochemical parameters and KFT between case and control is shown by Figure 2,3 and 4 respectively.

Table 2: Pearson Correlation with Hb, TLC, Platelet, HbA1c, S.Na, S.K, S.urea and S.creatinine with TmP/GFR

	Pearson Correlation	p-Value
Hb	-0.45	0.021
TLC	0.72	0.000
Platelet	0.41	0.036
HbA1c	-0.31	0.128
S.Na	-0.15	0.462
S.K+	0.41	0.040
S.UREA	0.63	0.001
S.CREATININE	0.11	0.584

Table 3: Pearson Correlation with Bilirubin, SGOT, SGPT and S. ALBUMIN with TmP/GFR

	Pearson Correlation	p-Value
Bilirubin Total	0.55	0.005
Bilirubin Indirect	0.53	0.005
Bilirubin Direct	0.53	0.005
SGOT	0.32	0.108
SGPT	0.41	0.038
S. ALBUMIN	-0.59	0.001

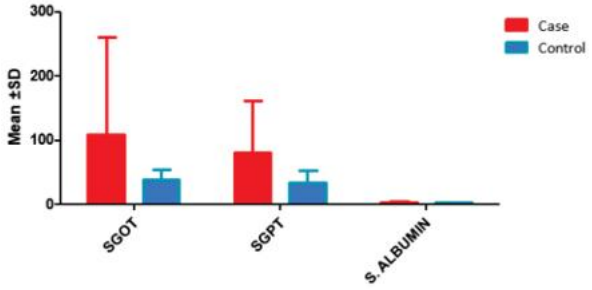

Figure 2: Shows the Association of Mean LFT Between Case and Control

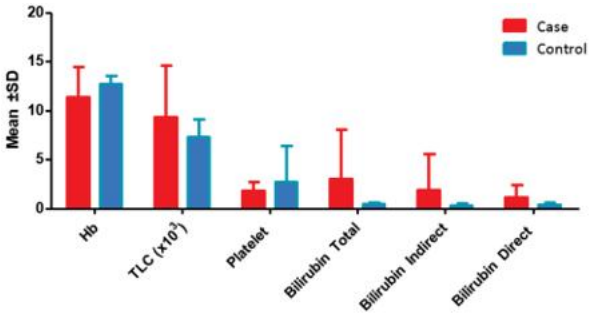

Figure 3: Shows the Association of Mean Biochemical Parameters Between Case and Control

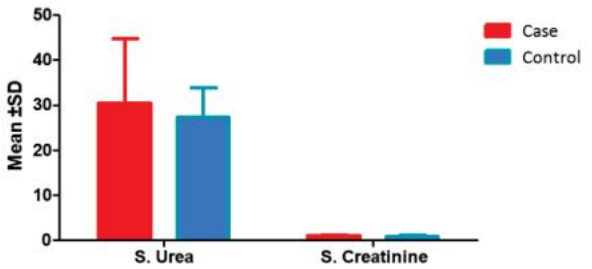

Figure 4: Shows the Association of Mean KFT Between Case and Control

DISCUSSION

Our study showed a mean TRP value of 97.14 ± 8.03 in the case group and 97.01 ± 8.00 in the control group. The TRP values were not significantly different between the groups. Our study showed no significant TRP difference between CLD

patients and healthy controls.

Chancharoenthana and Leelahavanichkul (2019) found that AKI in CLD patients is part of a broader spectrum of renal dysfunction that typically involves tubular injury before GFR changes are recognized.[6] Our results showed that altered TmP/GFR values indicate early tubular dysfunction which support the idea that standard eGFR measurements do not always represent renal injury in CLD.

According to Xiong et al. (2019) biomarkers of mild renal tubular dysfunction precede renal injury in critically ill cirrhotics.[7] The high TmP/GFR values in our study may indicate early-stage tubular changes that could exacerbate renal damage if left untreated.

Belmonte et al (2024)[8] found that cirrhotic individuals had a high frequency of clinically significant renal abnormalities, including tubular function, using a multiparametric renal function assessment. Our study found higher TmP/GFR in CLD patients, emphasizing the need for complete renal monitoring to gain therapeutically useful insights.

Dhayat et al (2019) found a renal phosphate leak phenotype associated with tubular dysfunction.[9] Although not directly related to CLD, the similarities in phosphate management and tubular dysfunction argue for TmP/GFR as a marker in our research group.

The mean TmP/GFR values in our study were 3.46 ± 0.79 for CLD patients and 2.50 ± 0.52 for healthy individuals. A significant difference in mean TmP/GFR values between groups ($t = 5.13$, $p < 0.001$) indicates impaired renal tubule function in CLD. Several studies have shown that impaired renal function is a common consequence of liver disease, sometimes preceded by a decrease in GFR.

Beben and Rifkin (2015) pointed out that conventional indicators may underestimate renal impairment in patients with liver disease, which complicates the calculation equations for GFR.[10] The elevated TmP/GFR in CLD patients in the present study may indicate renal dysfunction and supports the idea that tubular dysfunction can occur even with intact GFR.

Kumar et al (2021) reiterated that chronic renal dysfunction in cirrhosis, especially renal tubular abnormalities, is a major problem.[11] The elevated TmP/GFR of CLD patients may indicate tubular abnormalities, emphasizing the importance of indicators of tubular function. CLD patients often have impaired phosphate metabolism, which may explain the altered TmP/GFR in our study.

The results of van Londen et al. (2018) support TmP/GFR as a measure of tubular health.[12] Lower kidney donor TmP/GFR was associated with lower recipient GFR one year post-transplant, highlighting the importance of phosphate management on renal outcomes. In CLD, where renal function is often impaired, TmP/GFR may indicate early tubule damage.

These results suggest that TmP/GFR may be a useful marker of early renal tubular failure in CLD, providing a more nuanced view of renal health than classic GFR estimates.

Total bilirubin, indirect bilirubin and direct bilirubin showed moderately positive correlations with TmP/GFR ($r = 0.55$, 0.53 and 0.53, respectively; $p = 0.005$). These significant correlations indicate that TmP/GFR increases with bilirubin. Terg et al. (2010) found that liver and kidney function are linked in cirrhosis, and that elevated bilirubin levels are often associated with renal dysfunction.[13] SGOT has a modest positive correlation with TmP/GFR ($r = 0.32$, $p = 0.108$), although this is not significant. While, SGPT has a significant, moderate positive correlation with TmP/GFR ($r = 0.41$, $p = 0.038$). There may be a trend, SGOT alone cannot be indicative of TmP/GFR, however, this shows that TmP/GFR increases with liver inflammation or injury-induced elevated SGPT levels. Belmonte et al (2024) pointed out that liver enzyme values such as SGOT & SGPT are influenced by several variables and may not be indicative of renal function in patients with liver disease.[14] The inverse correlation between serum albumin and TmP/GFR is statistically significant ($r = -0.59$, $p = 0.001$). Due to reduced hepatic synthesis, liver disease lowers serum albumin and increases TmP/GFR. Kumar et al (2021) found that hypoalbuminemia indicates liver and kidney failure, especially in CLD.[15] In our data set, urinary phosphate (P04-) has no significant effect on TmP/GFR ($r = 0.01$, $p = 0.963$). Similarly, Dhayat et al. (2019) observed that urinary phosphate excretion is highly variable and may not accurately reflect systemic phosphate balance or renal function.[9]

Serum urea/TmP/GFR correlation higher serum urea levels are associated with higher TmP/GFR ratios ($r = 0.63$, $p = 0.001$). This indicates that phosphate processing in the kidney is closely related to urea, an important measure of renal function. De Araujo and Alvares-Da-Silva (2014) found that serum urea predicts renal outcomes in patients with liver disease.[16] Significantly, serum potassium correlates somewhat with TmP/GFR ($r = 0.41$, $p = 0.040$). Higher potassium levels improve TmP/GFR, indicating an involvement of potassium in renal tubule function. Our results were supported by Jawid and Subramanian (2017), who reported that electrolyte abnormalities, especially potassium levels, impaired renal function in cirrhotic individuals.[17] In conclusion compensated CLD patients had significantly higher TmP/GFR values than the control group, suggesting renal tubular dysfunction. This shows that early compensated CLD patients may have proximal renal tubular failure, which may indicate renal involvement.

We found modest associations between TmP/GFR and biochemical indicators such as age, hemoglobin and lipid profiles, indicating the complicated interaction between liver and renal systems in CLD. The study underscores the need for frequent testing of renal tubule function in CLD patients to detect dysfunction early and prevent the development of liver and kidney disease and improve quality of life.

Aknowledgement

It is a pleasant opportunity to express this note of thanks to all those without whose guidance, help and participation this work would not have been possible. First of all, I would like to thank the Almighty who gave me the opportunity and intelligence to do this work. I will always remain obliged to Him for giving me the parents who sacrificed their own comforts in making me what I am. I also thank Him for giving me the teachers who guided me out of darkness by their own radiant light. It has been a privilege to undertake this thesis under the most invaluable supervision of my respected Chief guide Prof. ARVIND GUPTA, Professor & Head, Department of Nephrology, Moti Lal Nehru Medical College, Prayagraj. The present work owes its inception, completion and success to his abiding interest which enabled this mammoth task to arrive into this presentable form. I am indebted to him for his boundless help, patience, clinical acumen, continuous guidance, vigilant supervision and subtle criticism without which this project would not have seen the light of the day. With extreme gratitude and respect, I express my indebtedness to my co guides Dr Garuav Garg, Dr. Upma Narayana, Dr. Santosh Maurya. Their excellent guidance and supervision enabled me to perform my very best in terms of work in the department and during the structuring of this thesis. Words cannot express the deep and precious feelings towards my Father Mr. Suresh Chand, my mother Mrs Santosh Devi and

my siblings Without a doubt, I could not have achieved anything in my life without their blessings and support. Dr. Shreya Dastidar who always cooperated with me in every phase of the work.

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