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Estimated Glomerular Filtration Rate (eGFR) Values as Predictor of Renal Insufficiency in Advanced Stages of Liver Diseases with Different Etiology

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ABSTRACT

Background: Various complications occur in patients with advanced stages of liver diseases. Renal dysfunction, a parameter included in the MELD score, is the most important prognostic factor. There is a strong need in clinical practice to estimate the GFR in this patients. **Objectives:** The aim of our study was to detect differences in renal function among patients with different stages of chronic liver diseases caused by HBV and HCV, also to determine the impact of viral etiology and gender on the values of eGFR and renal function. **Patients and Methods:** This was an observational cross-sectional study performed on patients with HBV and HCV chronic hepatitis, cirrhosis and HCC caused by these viruses hospitalized during period 2009–2014 in the Clinic of Gastroenterohepatology, Clinical Center University of Sarajevo. The estimated GFR (eGFR) was evaluated by the MDRD4 method. For the processing of data SPSS 21.0 statistical software was used. Statistical methods used in this study where: analysis of variance test (ANOVA test), Student's t-test for independent samples and Pearson coefficient of correlation. The level of significance was $p < 0.05$. **Results:** Among this three groups of patients there was a statistically significant difference in eGFR ($F = 18.79$, $p<0.05$), i.e. increase of degree of liver damage was related with increase of renal impairment, as reflected by a significant reduction in estimated glomerular filtration rate. Gender had no significant effect on eGFR and renal function ($p>0.05$), except in group of patients with HCC ($p<0.05$). Etiology had no significant effect on eGFR and renal ($p>0.05$).There was statistically significant inverse correlation between glomerular filtration rate and liver enzymes AST (-.184) and GGT (-.181). **Conclusions:** By calculation of GFR, we determined the existence of a significant reduction of kidney function through progression of liver damage from HBV and HCV chronic hepatitis, liver cirrhosis to HCC caused by these viruses, which drawing attention to the importance of the assessment of renal function in patients with this liver pathologies. Gender and etiology had no significant effect on eGFR and impairment of renal function. Given the statistically significant inverse correlation between eGFR and AST and GGT this liver enzymes may have important role as marker for both renal and hepatic injury.

Key words: renal and hepatic injury, renal insufficiency, eGFR.

1. BACKGROUND

Impairment of renal function is a common complication in liver dysfunction and significant source of morbidity in patients with advanced stages liver diseases (1, 2). Both acute and chronic renal dysfunction is common in end stage liver disease (ESLD). In 2007, approximately 7% of transplant candidates were on renal replacement therapy (RRT) listed for simultaneous liver-kidney transplant (SLK) or both (3).

In patients with advanced cirrhosis, not only hepatocellular carcinoma but also bacterial infections, such as spontaneous bacterial peritonitis (SBP) or pneumonia, are frequent clinical complications. These pathologies often progress to renal dysfunction. Advanced chronic liver disease is responsible for a significant number of physiological changes that affect the circulation and kidney perfusion. Hepatorenal syndrome (HRS) is caused by intense vasoconstriction of the renal circulation, which leads to a pronounced reduction in glomerular filtration rate (GFR). Although HRS was described more than 50 years ago, many features of its pathogenesis and natural history remained unknown for many years. No effective treatment

existed until very recently (4-7). Measuring kidney function reliably, noninvasive and reproducibly is the objective which should be reached and it is of particular importance for patients with comorbidities such as cirrhosis (8). Various estimating equations have been developed, but Modification of Diet in Renal Disease (MDRD) formula to estimate the GFR is the most used of the existing formulas for providing an assessment of kidney function which corresponds to the actual measurement of the GFR (9, 10). Despite its limitations in patients with cirrhosis, serum creatinine is universally used to assess renal function in clinical practice and as part of the MELD score for prioritization of recipients for liver transplantation (11).

2. OBJECTIVES

The aims of our study were to detect differences in renal function among patients with different stages of chronic liver diseases caused by HBV and HCV, also to determine the impact of viral etiology and gender on the values of eGFR and renal function.

3. PATIENTS AND METHODS

This was an observational cross-sectional study performed on patients with HBV chronic hepatitis, HCV chronic hepatitis, cirrhosis and HCC caused by these viruses hospitalized during period 2009–2014 in the Clinic of Gastroenterohepatology, Clinical Center University of Sarajevo. We identified 214 patients, 68 patients with HBV and HCV chronic hepatitis, 76 patients with cirrhosis and 70 patients with HCC caused by these viruses. All patients were diagnosed clinically, by laboratory analysis and histopathology. All patients underwent liver functional tests and AFP as marker of HCC. Patients underwent abdominal ultrasonography and computerized tomography too. Then the percutaneous and targeted liver biopsy histologicaly confirmed chronic active hepatitis B and/or C and HCC. Serum creatinine was measured by a modified Jaffe reaction. The estimated GFR (eGFR) was evaluated by the MDRD4 method according to the listed formula:

$$eGFR\ (mL/min/1.73\ m^2) = 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742\ if\ female) \times (1.212\ if\ African\ American)$$ (12, 13).

All patients who did not have complete diagnostic procedures in medical records, i.e. who did not have significant and necessary parameter for study, were excluded from it.

3.1. Statistical analysis

For the processing of data SPSS 21.0 statistical software was used. Categorical data were expressed as proportions (%), and continuous data as means ± standard deviation (SD). Statistical methods used in this study where: analysis of variance test (ANOVA test), Student's t-test for independent samples and Pearson coefficient of correlation. The level of significance was $p < 0.05$.

4. RESULTS

A total of 214 subjects, divided into three groups: 68 patients with HBV and HCV chronic hepatitis, 76 patients with cirrhosis and 70 patients with HCC caused by these viruses. The Table 1 shows the basic demographic parameters of subjects per group, which were not significantly different by group.

Diagnosis	Hepatitis	Cirrhosis	HCC
No. of patients	68	76	70
Age, years, Mean min max	46.60±11.342 19 72	61.13±12.129 27 90	63.84±9.821 42 86
Gender, No.(%)			
Male	44 (64.70%)	44 (57.89%)	37 (52.85%)
Female	24 (35.30%)	32 (42.11%)	33 (47.15%)
Etiology, No. (%)			
HBV	30 (44.11%)	45(59.21%)	34(48.57%)
HCV	38 (55.88%)	31 (40.79%)	36 (51.43%)

Table 1. The Number, Age, Gender Distribution, Relative Frequency of the Patients With HBV and HCV chronic hepatitis, cirrhosis and HCC caused by these viruses.

Sixty-eight patients, 44 (64.70%) M, 24 (35.30%) F, mean age 46.60 ± 11.342 years, presented with HBV (30 or 44.11%) or HCV (38 or 55.88%) chronic hepatitis. Seventy-eight patients, 44 (57.89%) M, 32 (42.11%) F, mean age 61.13 ± 12.129 years, presented with cirrhosis secondary to HBV (45 or 59.21%) or HCV (31 or 40.79%) infection. Seventy patients, 37 (52.85%) M, 33 (47.15%) F, mean age 63.84 ± 9.821, presented with hepatocellular carcinoma (HCC) secondary to HBV (34 or 48.57%) or HCV (36 or 51.43%) infection.

The eGFR of the patients is presented in Table 2 and Figure 1. A simple analysis of variance, ANOVA, revealed statistically significant differences between groups of patients with HBV and HCV chronic hepatitis, cirrhosis and HCC caused by these viruses in eGFR **($F= 18.79$, $p<0.05$)** (Table 2).This difference was specially expressed between the group of patients with chronic hepatitis and the group of patients with cirrhosis (Figure1). Figure1, graphic representation of arithmetic means in eGFR of patients, reveals a clear linear decline in eGFR values with the progression from chronic hepatitis to cirrhosis

Diagnosis	Hepatitis	Cirrhosis	HCC	F	p
eGFR (mL/min/1.73m²) Mean ± SD	97.94 ± 19.19	73.30 ± 28.33	73.92 ± 31.72	18.79	< **0.05**

Table 2. Mean EGFR values per groups ((HBV and HCV chronic hepatitis, cirrhosis, and HCC caused by these viruses) and ANOVA test results

The distribution of kidney disease stage's frequencies in groups (HBV and HCV chronic hepatitis, cirrhosis and HCC) is shown at Figure 2 where the frequency of more advanced kidney disease stages (3, 4, 5) increases with the severity of liver damage.

The kidney disease stages are mainly based on estimated GFR (Glomerular Filtration Rate). There are five stages where kidney function is physiological in stage 1, and minimally reduced in stage 2. The normal kidney function (eGFR > 90) was most frequent in patients with chronic hepatitis and that the incidence of this stage decreased with the degree of liver damage (23 patients with cirrhosis, 20 patients with HCC) as is presented in Figure 2.. Mildly reduced kidney function (stage 2) was also present in patients with hepatitis (18 patients or 26.47%), which indicates the abundance of beginning of kidney damage at

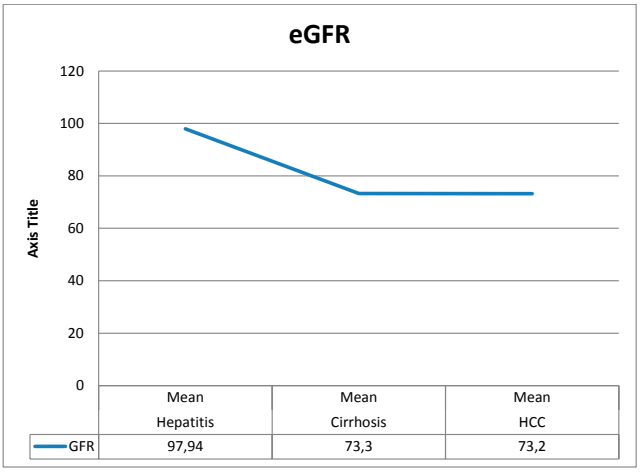

Figure 1. Graphic representation of arithmetic means in egfr of patients grouped according to the degree of chronic liver damage (hbv and hcv chronic hepatitis, cirrhosis, and hcc caused by these viruses)

the lowest degree of liver damage. Only one patient with hepatitis had moderately reduced kidney function (stage 3), while this kind of kidney damage was with greater frequency present in patients with a higher degree of liver damage, (16 patients or 21.5% of patients with cirrhosis, and a 17 patients or 24.28% of patients with HCC). Severely reduced kidney function, did not have any patient with hepatitis while this kidney damage was adequately represented (with a frequency of 10 %) in patients with end-stage liver damage, and patients with cirrhosis had a slightly lower incidence (3.49 %). Very severe, or end-stage kidney failure (sometimes call terminal renal failure) did not exist in the group of patients with hepatitis but only in patients with a higher degree of liver damage, with a total of 5 patients with cirrhosis and HCC. The frequency of pathological stage increases with the degree of liver damage, i.e. the increase in renal function damage was accompanied by an increase in liver function damage, as presented in Figure 2.

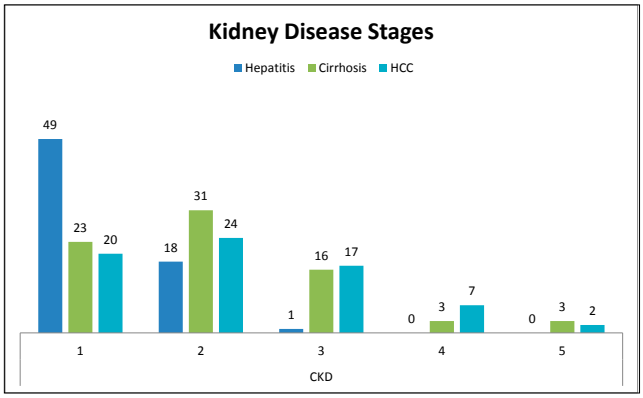

Figure 2. Distribution of the frequency of different kidney disease stages

We found the lack of statistically significant differences **(p>0.05)** between genders within the group of patients with HBV and HCV chronic hepatitis and cirrhosis, while this difference was significant in the group of patients with HCC (Figure 3). There was also no significant difference (**p> 0.05**) between HBV and HCV etiology in eGFR within the groups of patients with HBV and HCV chronic hepatitis, cirrhosis and HCC caused by these viruses.

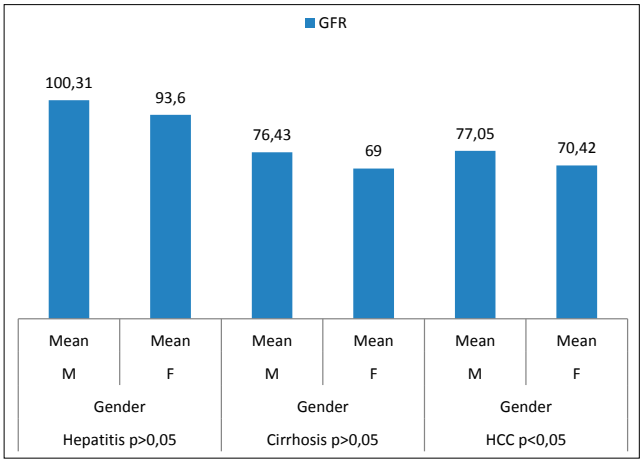

Figure 3. The EGFR according to etiology

There was significant correlation between eGFR and gama-glutamil transferase (GGT) and aspartate aminotransferase (AST) which was the reverse, i.e. increase in serum concentrations of these liver enzymes is followed by reduction in eGFR. There was no established significant correlation between eGFR and alanine aminotransferase (ALT). In this way, we indirectly determine the correlation between the degree of hepatic and renal dysfunction.

Pearson's Correlation	eGFR	AFP	AST	ALT	GGT
eGFR	1	.144	-.184**	-.114	-.181*

Table 3. Correlation between EGFR and liver enzymes. **. Correlation is significant at the 0.01 level (2-tailed).*. Correlation is significant at the 0.05 level (2-tailed).

5. DISCUSSION

Various complications occur in patients with advanced stages of liver diseases. Renal function in patients with advanced stages of liver diseases is important parameter which lead to a prioritization of liver transplant allocation towards patients with renal dysfunction, and reduce mortality among patients awaiting liver transplantation (8).

Serum creatinine is the most used method for assessing renal function in patients with advanced stages of liver diseases. The inulin clearance which is the global standard measurement for GFR, can reflect GFR correctly, but repeat measurement is difficult clinically because the method is very complicated. Other biomarkers, such as cystatin C also appear to have errors. Despite promising results with the use of cystatin C, Xirouchakis stated in a recent paper that the estimated GFR in cirrhosis is not better with cystatin C formulas compared to creatinine ones (14). Hence, attempts to estimate GFR from serum creatinine for screening purposes should be undertaken despite limitations in calculating equations (MDRD4 in our case). Number of different equations have been derived that incorporate this parameter to provide an estimation of the GFR: Cockroft-Gault (C-G), MDRD, and CKD-EPI. Both C-G and MDRD have limitations in patients with cirrhosis, and the utility of the CKD-EPI equation in patients with cirrhosis has not yet been proven although Chen and colleagues demonstrated that the eGFR calculated by the MDRD equation may be closer to the true GFR than that calculated by the CKD-EPI equation (15). These equations should never

be employed in patients with acute kidney injury. Still, the MDRD4 formula is widely used in clinical practice for population screening. Despite its limitations in patients with cirrhosis, because serum creatinine within the normal reference range does not exclude a significant impairment in the GFR, there is a strong need in clinical practice to estimate the GFR in patients with advanced stages liver diseases.

The aim of our study was to detect differences in renal function in patients with different stages of chronic liver damage caused by HBV and HCV. We found that HBV chronic hepatitis, HCV chronic hepatitis, cirrhosis and HCC secondary to these viruses were associated with a reduction of the eGFR (Table 2). We also found that among this three groups of patients there was a statistically significant difference in eGFR ($F= 18.79$, $p<0.05$), i.e. increase of degree of liver damage is related with increase of renal impairment, which was reflected by a significant reduction in estimated glomerular filtration rate. Figure 1 clearly shows a linear reduction in glomerular filtration rate accompanied by progression from chronic hepatitis to cirrhosis which drawing attention to the importance of the assessment of renal function in patients with chronic hepatitis and cirrhosis. Our results are in agreement with the very recent results of Gluhovschi et al. (16).

Moderately reduced kidney function was present with significantly greater frequency in patients with a higher degree of liver damage, 16 patients or 21.5% of patients with cirrhosis, and the 17 patients or 24.28% of patients with HCC had this stage of renal dysfunction. Severely reduced kidney function was adequately represented (with a frequency of 10 %) in patients with end-stage liver damage, and patients with cirrhosis had a slightly lower incidence (3.49 %). Exactly a type-2 HRS is characterized by moderate/severely renal damage, and this type of HRS is gradually progressive and arises in association with the progression of cirrhosis. Patients with type 2 HRS are at particularly high risk for type 1 (17). Very severe, or end-stage kidney failure (sometimes call established renal failure) exist only in the group of patients with a higher degree of liver damage (with a total of 5 patients with cirrhosis and HCC). Our results are in agreement with the results of Gines et al. (18) and Shepke et al. (19).

We found that gender and etiology had no significant effect on eGFR in the group because during our analysis we did not find a statistically significant difference (Figures 2 and 3). There is a paucity of data in the literature regarding HBV infection and renal function, while data on renal function in HCV infection is conflicting. Some authors, such as Tsui and Arsiani found no association between HCV and kidney disease (20, 21), while Dalrymple reported that HCV was associated with an increased prevalence of renal insufficiency (22). Fabrizi et al. have recently performed a meta-analysis of published medical literature and pooling of study results demonstrated the absence of an association between HCV seropositive status and reduced estimated GFR (23). Establishing the existence of a statistically significant inverse correlation between glomerular filtration rate and liver enzymes (-.184** and -.181*) illustrates a statistically significant correlation between the renal and hepatic insufficiency. These results are unique as there are no similar in the existing literature.

6. CONCLUSIONS

By calculation of GFR, we determined the existence of a significant reduction of kidney function in patients with liver damage caused by chronic viral hepatitis, liver cirrhosis and HCC by viral etiology, which drawing attention to the importance of the assessment of renal function in patients with this liver pathologies. Gender and etiology had no significant effect on eGFR and impairment of renal function. Given the statistically significant inverse correlation between eGFR and AST and GGT, this liver enzymes may have important role as marker for both renal and hepatic injury.

CONFLICT OF INTEREST: NONE DECLARED

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