The Role of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in the Evaluation of Renal Functions in Patients with Liver Cirrhosis

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Abstract

Aim: Early diagnosis of renal dysfunction has clinical and prognostic importance for liver cirrhosis. The disadvantages are that creatinine and blood urea nitrogen (BUN) are dependent on age and muscle mass in demonstrating renal dysfunction. There is a need for parameters that can detect renal dysfunction early in cirrhotic patients. Our aim was to investigate the sensitivity, specificity and predictive value of serum Neutrophil Gelatinase Associated Lipocalin (NGAL), serum creatinine and BUN levels against glomerular filtration rate (GFR) in the evaluation of renal function in Child A and Child B liver cirrhosis patients.

Methods: This study was conducted in a total of 84 patients with Child A or Child B liver cirrhosis who were admitted to the gastroenterology clinic between 2009 and 2010. The study was based on retrospective review of the patients' files. Clinical and laboratory parameters were recorded.

Results: We found that serum NGAL 45.8%, creatinine 88.5% and BUN 84.2% positive predictive value in defining GFR for all patients in Child A and B stages. In our study, we concluded that a NGAL value of 114.17 ng/ml and above has 68.75% sensitivity and 50% specificity in indicating glomerular filtration rate. The diagnostic utility was 47.4% and it was not found significant (p= 0.053).

Conclusions: It has been shown that serum creatinine values are more sensitive and specific than BUN and a new marker, NGAL, in terms of predicting the changes that may occur in the GFR of patients in Child A and B stages.

Keywords: *Liver cirrhosis; renal functions; NGAL*

1. Introduction

Liver cirrhosis is a chronic, diffuse and progressive liver disease characterized by loss of normal parenchymal tissue, increase in connective tissue, formation of regeneration nodules and deterioration of the vascular structure. Clinically, it is a fatal disease with hepatocellular failure and portal hypertension findings.[1] Loss or impairment of renal function is a common problem in cirrhotic patients. Renal dysfunction in cirrhotic patients worsens the prognosis, so much so that creatinine value as well as serum bilirubin and INR values are used as parameters in the MELD (Models for End Stage Liver Disease) score, which is used to predict the prognosis of patients who will undergo liver transplantation.[2]

As cirrhosis progresses to the decompensated stage, circulatory disturbance worsens, splanchnic vasodilatation becomes more pronounced and sympathetic nervous system and renin-angiotensin activity increase to maintain hemodynamic balance. Despite the increase in natriuretic substances, sodium retention, ascites and peripheral edema occur. Despite the increase in various vasoconstrictor substances in the early stages of ascites formation, renal perfusion and GFR may be normal or slightly decreased. This is due to increased renal prostaglandin production.[3] As splanchnic and systemic vasodilatation continues due to hyperdynamic circulation, systemic arterial pressure decreases and this leads to decreased renal blood flow, renal vasoconstriction develops and GFR decreases.[4] Hepatorenal syndrome (HRS) occurs in the advanced stages of cirrhosis and in the period when circulatory disturbance is the highest. In this picture, renal vasoconstriction occurs as a result of increased intrarenal vasoconstrictor substances and GFR falls below 40 ml/min/1.73m^2. The kidney is histologically normal in patients with

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hepatorenal syndrome.[5] HRS is found in 7% to 15% of patients hospitalized for cirrhosis. It is characterized by oliguria, azotemia, hyponatremia and low urinary sodium. The diagnosis of HRS can only be made after other causes of renal failure are ruled out.[6] There are 2 types of HRS. Type 1 HRS is characterized by rapid and progressive renal failure, associated with other medical complications and therapeutic interventions, an increase in serum creatinine above 2.5 mg/dl in less than 2 weeks and a decrease in creatine clearance to 20ml/min. Type 2 HRS is a slowly progressive renal impairment characterized by a stable to moderately decreased GFR with relatively well preserved liver reserve and function and has a better prognosis.[7] In one study, it was shown that 18% of 234 non-azotemic patients with cirrhosis and ascites developed functional renal failure (HRS) within 1 year and 39% within 5 years.[8] Plasma creatinine measurement is the standard biochemical test to evaluate renal function. Plasma creatinine level does not have a linear relationship with GFR. In 30% of patients with significant renal dysfunction, plasma creatinine remains within normal limits. Muscle mass accounts for 98% of the total body creatine pool. Changes in body composition due to gender, race and age, exercise and muscle diseases affect the rate of creatinine formation and alter plasma creatinine concentration and urinary creatinine excretion.[9] NGAL is a 25-kDa, 178 amino acid glycoprotein found in neutrophil granules and is an activation modulator of matrix metalloproteinase.[9] NGAL was first detected as a colorless or slightly rose-colored staining protein on E.coli bacteria.[10] NGAL belongs to the Lipocalin superfamily and is also known as Lipocalin 2. NGAL is released from renal tubular cells, hepatocytes and immune cells in various pathological conditions. As one of the effector molecules of the immune system, it has also been found to be an important modulator of cell homeostasis.[10] NGAL is the most promising biomarker for early detection of acute kidney injury and is easily excreted and detected in urine. Because it is molecularly small and resistant to degradation. NGAL accumulates in human renal cortical tubules and urine after nephrotoxic and ischemic injury. This means that NGAL is an early sensitive and non-invasive biomarker for acute renal injury.[11]

This study aims to investigate the sensitivity, specificity, and predictive value of serum Neutrophil Gelatinase-Associated Lipocalin (NGAL), serum creatinine, and BUN levels in evaluating renal function in patients with Child A and Child B stage liver cirrhosis.

2. Materials and Methods

This study was conducted in a total of 84 patients with Child A or Child B liver cirrhosis who were admitted to the gastroenterology clinic between 2009 and 2010. The study was based on a retrospective chart review. Patients with signs or symptoms of systemic infection or inflammation, elevated C-Reactive protein, suspected or confirmed malignancy, active bleeding, impaired thyroid function, comorbid pathologies such as diabetes mellitus, hypertension and coronary artery disease that may affect renal function, GFR of 40ml/minute or less, which is considered the limit for hepatorenal syndrome, and cirrhosis of the liver in Child C class were excluded. Age, gender, race and serum creatinine values were used to calculate the GFR of the patients by using the MDRD (Modification of Diet in Renal Disease) formula. The control group consisted of 28 patients of similar age and gender, 14 females and 14 males, with a mean age of 44.6±12.8 years, GFR ≥90 ml/min/1.73m^2, normal liver function and no comorbidities. Eighty-four patients were evaluated quantitatively for age, serum creatinine, GFR, albumin, bilirubin, INR, CRP and NGAL values and qualitatively for gender, presence of ascites and encephalopathy and distribution of patients according to Child classification. Gender, age, BUN, creatinine and NGAL levels were used in the descriptive characteristics of 28 individuals who constituted the healthy control group.

Statistical calculations were performed using SPSS 9.0 computer program. Student t test (Mann-Whitney U test when necessary), Chi-square and Kruskal-Wallis test were used for statistical analysis. P<0.05 was considered statistically significant.

3. Results

A total of 84 patients between the ages of 25 and 85 years, 32 (38.1%) females and 52 (61.9%) males, were included in the study. There were 48 patients (57.1%) in Child-A group and 36 patients (42.9%) in Child-B group. There were 52 (61.9%) patients with GFR >90ml/min and 32 (38.1%) patients with GFR 40-89 ml/min. Encephalopathy was not detected in any patient and ascites was present in 18 (21%) patients. The distribution of the patients included in the study according to gender, GFR, presence of ascites and cirrhosis stage is given below (Table-1).

Table 1

Distribution of patients according to gender. GFR. presence of ascites and Child classification

		n	%
Gender	Male	52	61.9%
	Female	32	38.1%
	Total	84	100.0%
GFR	40-89 ml/mn	32	38.1%
	>90ml/mn	52	61.9%
	Total	84	100.0%
Ascites	Yes	18	21.4%
	No	66	78.6%
	Total	84	100.0%
Child	A	48	57.1%
	B	36	42.9%
	Total	84	100.0%

GFR: Glomerular Filtration Rate; Child: Child-Pugh Classification (used for cirrhosis severity); n: Number of patients.

Age, BUN, serum creatinine, GFR, serum albumin, INR, total bilirubin, CRP and NGAL values were compared between Child A and B groups according to Child staging. The difference between the two groups in terms of serum albumin, INR, CRP and total bilirubin was found to be significant (Table-2, p<0.05). Consistent with the clinical stage, INR, CRP and total bilirubin were found to be higher in the Child B group compared to the Child A group, while serum albumin value, which is an indicator of the function of the liver and a negative acute phase reactant, was found to be significantly lower in the Child B group.

Based on glomerular filtration rate, age, serum creatinine, albumin, INR, BUN, NGAL, CRP and total bilirubin values were compared in patients with GFR of 90ml/minute/1.73m^2 and above with preserved renal function and in patients with low clearance renal failure with GFR between 41-89ml/minute/1.73m^2 (Table 3). The mean age of the group with low GFR was significantly higher than the group with normal GFR. Serum creatinine and BUN levels were

significantly higher in the group with low GFR compared to the normal group. There was no significant difference in serum NGAL levels between the group with low GFR and the group with normal GFR.

Table 2

Averages of some basic parameters according to Child classification

		Child		P
		A (n=48)	B (n=36)	
Age	Mean	60.46	60.67	0.932
	SD	10.10	12.16	
GFR (ml/dk/1.73m2)	Mean	94.94	96.08	0.837
	SD	25.24	24.95	
Alb(gr/dl)	Mean	3.96	3.20	<0.001
	SD	.41	.64	
INR	Mean	1.17	1.31	0.003
	SD	.15	.24	
BUN (mg/dl)	Median	13.50	15.00	0.273
	IQR	7.00	9.00	
Creatinine(mg/dl)	Median	.74	.77	0.668
	IQR	0.23	0.18	
NGAL (ng/ml)	Median	135.66	117.98	0.832
	IQR	58.63	80.7	
CRP	Median	.30	.75	<0.001
	IQR	0.56	0.64	
T. Bil(mg/dl)	Median	1.10	2.20	<0.001
	IQR	0.70	1.85	

GFR: Glomerular Filtration Rate; Alb: Albumin; INR: International Normalized Ratio; BUN: Blood Urea Nitrogen; CRP: C-Reactive Protein; T. Bil: Total Bilirubin; NGAL: Neutrophil Gelatinase-Associated Lipocalin.

In all our patients with cirrhosis in Child A and B stages, a BUN value of 13mg/dl or less was shown to have a sensitivity of 65.5% and specificity of 85% in indicating a glomerular filtration rate of 90ml/min or more. Here, the diagnostic usefulness of BUN value was 69% and found to be significant (p<0.001). (Figure 1)

In all our patients with cirrhosis in Child A and B stages, a serum creatinine value of 0.79mg/dl

or less had a sensitivity of 88.4% and a specificity of 81% for glomerular filtration rate of 90ml/min or more. The diagnostic utility was 85.7% and was found to be significant (p<0.001). (Figure 2)

In all our patients with cirrhosis in Child A and B stages, NGAL values of 114.17 ng/ml and above had a sensitivity of 68.75% and specificity of 50% for glomerular filtration rate of 90ml/min and above. The diagnostic usefulness was 47.4%, which was not significant (p= 0.053). (Figure 3)

Figure 1

Diagnostic sensitivity of BUN value

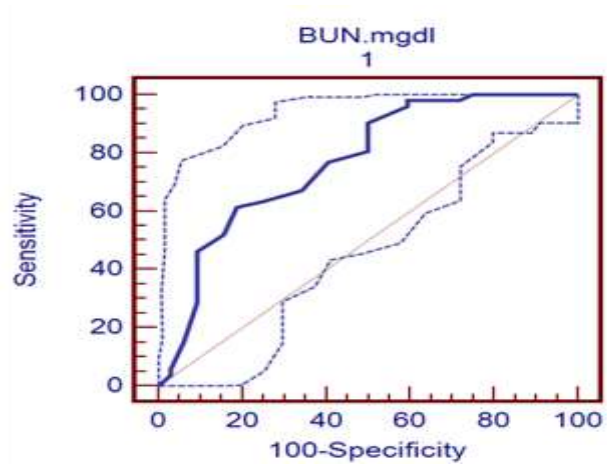

Figure 2

Diagnostic sensitivity of creatinine value

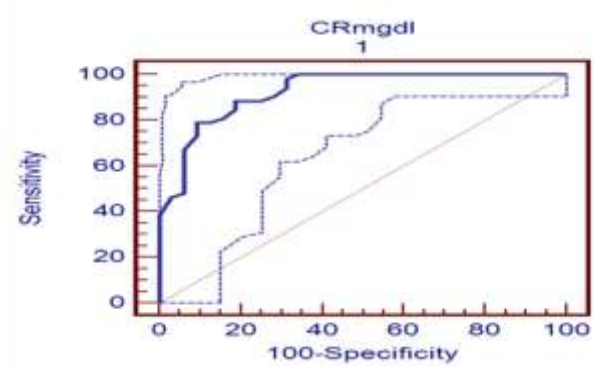

Figure 3

Diagnostic sensitivity of NGAL value

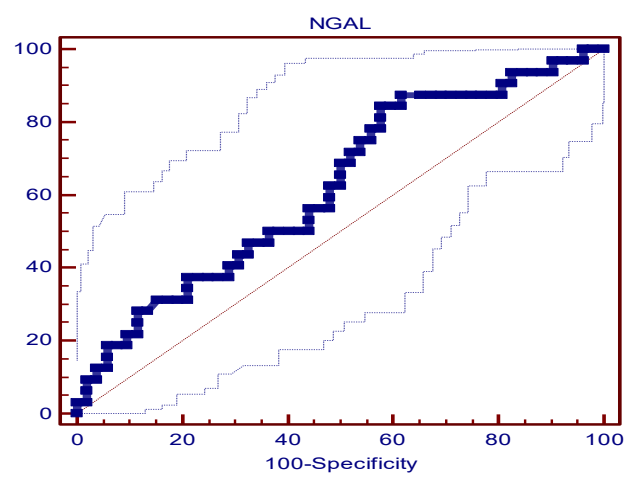

Table 3

Means, medians and distribution ranges of some basic parameters of patients classified according to GFR

		GFR		P
		40-89 ml/min (n=32)	≥90ml/min (n=52)	
Age	Mean	66.34	56.98	<0.001
	SD	7.06	11.46	
Creatinine (mg/dl)	Mean	.97	.70	<0.001
	SD	.19	.08	
Alb (gr/dl)	Mean	3.70	3.60	0.499
	SD	.71	.61	
INR	Mean	1.20	1.25	0.317
	SD	.19	.21	
BUN (mg/dl)	Median	18.00	12.00	<0.001
	IQR	8.00	6.00	
NGAL (ng/ml)	Median	140.01	115.96	0.062
	IQR	62.66	64.27	
CRP	Median	.57	.50	0.843
	IQR	0.73	0.63	
T. Bil (mg/dl)	Median	1.25	1.40	0.651
	IQR	1.65	1.25	

GFR: Glomerular Filtration Rate; Alb: Albumin; INR: International Normalized Ratio; BUN: Blood Urea Nitrogen; NGAL: Neutrophil Gelatinase-Associated Lipocalin; CRP: C-Reactive Protein; T. Bil: Total Bilirubin.

In a logistic regression analysis with renal failure as the dependent variable and age, creatinine, BUN and NGAL as independent variables, the risk of decreased glomerular filtration rate was found to be 23.9 times higher (OR 23.9, 95% CI 6.645-86.471, p<0.001) in patients with Child A and B stage liver cirrhosis above the cut-off value of 0.79mg/dl obtained for serum creatinine. (Table 4)

As a result of our study, it was determined that NGAL had a positive predictive value of 45.8%, creatinine 88.5% and BUN 84.2% for glomerular filtration rate of 90ml/min and above in patients with Child A and B stage liver cirrhosis included in the study.

4. Discussion

It is known that determination of GFR with formulas based on serum creatinine or creatinine clearance in patients with cirrhosis of the liver are not sensitive methods for optimal assessment of renal function.[12] Decreased muscle mass, anorexia, protein-restricted diet, severe hyperbilirubinemia, decreased creatinine formation in the KC, increased tubular secretion of creatinine, false low serum creatinine levels due to excessive fluid intake, and therefore false or high measurements of GFR or creatinine clearance may occur.

In our study, GFR calculated with the MDRD formula was used to evaluate renal function. This is because the MDRD formula does not include body weight. Since the MDRD formula is independent of body weight, it reflects the GFR more accurately than the GFR calculated using the Cocroft and Gault formula.[13]

Creatininee to creatinine conversion is reduced in patients with liver parenchymal disease. Decreased creatine production as a result of muscle wasting and malnutrition leads to lower basal serum creatinine levels in cirrhotic patients compared to the normal population, and as a result, normal serum creatinine levels in patients cannot exclude renal dysfunction. Muscle wasting and malnutrition were not significant in the stage of cirrhosis of the liver (Child A and B stages) of our patients included in the study and serum NGAL, creatinine and BUN were found to be positively predictive of GFR at 45.8%, 88.5% and 84.2%, respectively.

Table 4

Cut off, sensitivity, specificity, positive and negative predictive values for some of the basic parameters we evaluated in patients with liver cirrhosis in Child A and Child B stage and glomerular filtration rate of 90ml/min and above.

	Cutt Off	Sensitivity	Specificity	+PV	-PV	AUC±Se	Diagnostic Efficiency	Efficiency	P
Age , years	≤53 *	44.23	100	100	52.5	0.767±0.055	65.5	58.83	<0.001
Alb, gr/dl	≤4,3	96.15	21.87	66.7	77.8	0.538±0.064	67.9	28.94	0.559
BUN, mg/dl	≤13 *	61.54	81.25	84.2	56.5	0.770±0.055	69.1	59.29	<0.001
Cr, mg/dl	≤0,79 *	88.46	81.25	88.5	81.2	0.925±0.034	85.7	85.56	<0.001
CRP	≤1,19 *	92.31	21.87	65.8	63.6	0.513±0.065	65.5	26.32	0.843
INR	>1,12 *	78.85	43.75	69.5	56	0.555±0.064	34.5	30.80	0.391
NGAL, mg/dl	>114,17	68.75	50	45.8	72.2	0.622±0.0622	47.4	12.2	0.053
T.Bil, mg/dl	>0,7 *	86.54	25	65.2	53.3	0.529±0.064	36.9	27.98	0.649

Alb: Albumin; BUN: Blood Urea Nitrogen; CRP: C-Reactive Protein; INR: International Normalized Ratio; NGAL: Neutrophil Gelatinase-Associated Lipocalin; T.Bil: Total Bilirubin; GFR: Glomerular Filtration Rate; +PV: Positive Predictive Value; -PV: Negative Predictive Value; AUC: Area Under Curve; SE: Standard Error.

In our study, a positive but low but significant correlation was found between serum NGAL and creatinine and between serum NGAL and CRP. No significant correlation was found between serum NGAL levels and age, BUN, serum albumin, bilirubin and INR which are important in prognostic staging of chronic liver disease.

Researches on the use of NGAL in acute kidney injury has focused on two areas: The use of NGAL as an early marker of acute kidney injury and its association with short-term dynamic GFR changes (use in GFR estimation). Increases in NGAL have been associated with acute kidney injury and dynamic GFR changes in models of renal ischemia during major cardiac surgery, contrast agent-induced nephropathy, renal ischemia during and after acute myocardial infarction, and renal ischemia due to septic shock 14. In our study, since serum NGAL levels were targeted not to predict acute kidney injury due to chronic liver parenchymal disease in our patients, but to predict existing low clearance renal failure and normal renal function, NGAL is not expected to provide information about dynamic GFR change.

When the studies related with the use of NGAL in chronic kidney injury were examined, immediate and prospective NGAL levels were associated with GFR measured instantaneously or prospectively (in various time periods).[15]

In our study, the positive descriptive power of NGAL was lower than creatinine. This may be due to the fact that most of our patients (n=48, 57.1%) were in Child A prognostic stage, that is, patients with compensated cirrhosis. The absence of malnutrition and muscle mass loss in patients with compensated cirrhosis may have maintained the positive predictive power of creatinine. In addition, the fact that most of the patients included in our study (n=52, 61.9%) had normal GFR (>90ml/min/1.73 m) may have weakened the correlation between NGAL, creatinine and GFR. These results show that serum creatinine is more sensitive and specific than age, BUN and a new marker, NGAL, in predicting changes in glomerular filtration rate in patients with liver cirrhosis in Child A or B stage. As a result, it has been reported that the cost of NGAL is higher compared to creatinine, there is no normal range and serum NGAL measurement is affected by many different conditions.[15] More comprehensive and large studies are needed for NGAL to be accepted as the standard method in the evaluation of renal function loss in cirrhotic patients.

5. Conclusion

In this study, it was determined that serum creatinine values are more sensitive and specific than BUN and NGAL in predicting changes in the glomerular filtration rate in patients with liver cirrhosis at Child A or B stage. NGAL, although promising, showed lower predictive power in our cohort possibly due to the predominance of patients in the compensated stage of cirrhosis. Therefore, while NGAL might be useful in early detection of acute kidney injury, its role in chronic conditions such as cirrhosis-associated renal dysfunction needs further investigation. Future large-scale and prospective studies are necessary to establish NGAL as a standard marker for renal function assessment in cirrhotic patients.

Statement of ethics

This thesis study, which was conducted using retrospective patient records, was carried out without obtaining consent, as there was no ethical approval requirement at the time of publication.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers.

Author contributions

Concept: EK, MA Design: EK, MA, MP, ST, DES, Data Collection or Processing: EK Analysis or Interpretation: EK, MA, MP, Literature Search: EK, MA Writing: EK, MA

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