International Journal of Research and Review
Vol. 9; Issue: 1; January 2022
Website: www.ijrrjournal.com
Original Research Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

The Difference of Urinary Neutrophil Gelatinase-Associated Lipocalin Level between Liver Cirrhosis Patients with and without Hepatorenal Syndrome

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DOI: https://doi.org/10.52403/ijrr.20220101

ABSTRACT

Objective: To determine differences of urinary Neutrophil Gelatinase-Associated Lipocalin level in liver cirrhosis patients with or without Hepatorenal Syndrome (HRS).
Methods: This study was conducted on 46 liver cirrhosis patients (20 patients without hepatorenal syndrome, 26 patients with hepatorenal syndrome). Diagnosis of HRS was based on International Ascites Club criteria. Urinary NGAL was examined using ELISA method. Data analysis was performed with p<0,05 stated as statistically significant.
Result: This study showed more HRS cases was found in male than female, with an average age of 53,95 years old for hepatic cirrhosis without HRS, and 57,35 with HRS. The most common cause of this study is Hepatitis B virus, and the highest grade of severity is in Child Pugh-C. The average urinary NGAL level in liver cirrhosis with HRS is 59,39 ± 58,98 ng/ml and 130,78 ± 45,14 ng/ml in liver cirrhosis without HRS.
Conclusion: There was a significant higher urinary NGAL level in liver cirrhosis with HRS (p = 0.000), with the cut-off of urinary NGAL to differentiate cirrhosis patients with and without HRS was 95,115 ng/ml.

Keywords: NGAL, HRS, hepatorenal syndrome, neutrophil gelatinase-associated lipocalin

INTRODUCTION

Liver cirrhosis (hepatic cirrhosis) is a chronic disease in which the micro-circulation, the anatomy of large blood vessels and the entire architectural system of the liver become irregular caused by the addition of connective tissue (fibrosis) around the regenerating liver parenchyma.[1] Liver cirrhosis is the third highest mortality cause in patients between the age of 45-46 years old. Common cause of cirrhosis are alcoholic liver disease, non-alcoholic steatohepatitis and also hepatitis C.[2] The etiology of hepatitis may vary, with more than 1 cause could present in one patients. Another etiology of hepatitis are hepatitis virus (B,C and D), alcohol consumption, metabolic disease, hemochromatosis, Wilson's disease, cholestasis, Budd-Chiari syndrome, hepatic vein obstruction, and et cetera.[3.4]

Hepatic cirrhosis (HC) caused by chronic-reversible injury on the liver parenchyma, along with diffuse connective tissue and the formation of degenerative nodule in micro nodules up to macro nodules. Deposit of extracellular matrix (ECM), which produced by stellate cells, in space of disease will make changes in shape and stimulate the blood vessel capillarization. Sinusoidal capillarization then altered the normal exchange of portal

vein and hepatocyte, so materials that should be metabolized by hepatocytes will directly enter the systemic blood stream and inhibit materials produced by the liver from entering the blood. The whole process will cause portal hypertension and decrease in hepatocellular function.[3,4] The clinical manifestations of progressive hepatocellular dysfunction in cirrhosis are similar to acute or chronic hepatitis, including symptoms such as signs of fatigue, lack of enthusiasm, weight loss, GI disturbances with signs of nausea, vomiting, jaundice, hepatomegaly and extrahepatic symptoms with signs of erythema. palmar, spider angiomas, muscle atrophy, parotid and lacrimal gland enlargement, gynecomastia and testicular atrophy in men, menstrual disorders in women and coagulopathy.[5]

The diagnosis of cirrhosis is based on physical examination and further laboratory tests. Physical examination in decompensated stage may show the presence of ascites, pretibial oedema, splenomegaly, collateral veins and palmar erythema. Common findings in further laboratory test on cirrhosis patients are[6] :

1. Abnormal aminotransferase
2. Elevated Alkaline phosphatase level
3. Elevated Gamma Glutamyl Transpeptidase (GGT) level
4. Elevated Bilirubin serum in accordance with disease progressivity
5. Hypoalbuminemia, not specific for liver disease, but albumin level might be used to determine cirrhosis severity.
6. Prolonged prothrombin time (PT)
7. Other liver function laboratory tests, such as hyponatremia, thrombocyto-penia, acute anaemia (normochromic), leukopenia, neutropenia, et cetera.

Ultrasonography examination is likely the choice for diagnostic, as it is a non-invasive examination with high accuracy. However, it has limitation to diagnose in the early stage. Serial ultrasound examination could assess the development and detect hepatocellular carcinoma in early stage. Gold standard in diagnosing HC is biopsy followed by histopathology examination.[7,8] Options in scoring assessment for disease severity are Child-Turcotte-Pugh score or MELD score.[9]

Table 1 Prognosis Assessment in Cirrhosis : Child-Turcotte-Pugh Score

Parameter	**Numeric Scoring**		
	1	**2**	**3**
Ascites	None	Mild	Intermediate to Severe
Hepatic Encephalopathy	None	Grade 1-2	Grade 3-4
Bilirubin, mg/dl (mcmol/L)	<2,0 (<34,2)	2-3 (34,2-51,3)	>3,0 (>51,3)
Albumin, g/dL (g/L)	>3,5 (35)	2,8-3,5 (28-35)	<2,8 (28)
Prothrombin Time (sec)	1-3	4-6	>6

Table 2. Classification for Numeric Scoring with Child Turcotte Pugh Score

Score	**Class**
5-6	A
7-9	B
10-15	C

Management of HC can be symptomatic, supportive and specific treatment depends on the etiology. The following table shows the specific treatment for liver cirrhosis[4]:

Table 3. Specific Treatment of Cirrhosis

Etiology	**Therapy**
Hepatitis virus (B dan C)	Antivirus
Alcohol consumption	Quit or reduction of alcohol consumption
Non-alcoholic Steatohepatitis (NASH)	Weight loss
Metabolic syndrome: 1. Hemochromatosis 2. Wilson's disease 3. Alpha-1-antitrypsin deficiency 4. Galactosemia 5. Tyrosinemia	 Phlebotomy Copper Chelator Transplantation Reduce dairy product and tyrosin consumption
Autoimmune Hepatitis	Immunosuppressive drugs
Toxin, Drugs	Identify the toxin or any underlining drugs causing liver cirrhosis, followed by discontinue consumption of those product.

Untreated HC could lead into several complication, such as portal hypertension, hepatorenal syndrome, ascites, spontaneous bacterial peritonitis (SBP), hypoalbuminemia, peripheral oedema, hepatic encephalopathy, and et cetera.[10] Hepatorenal syndrome (HRS) usually caused by vasoconstriction of renal circulation, followed by reduced filling of systemic artery caused by vasodilatation of splenic circulation. There are three dominant factors involved in HRS pathogenesis[11]:

1. Haemodynamic changes; massive vasodilatation of peripheral artery with hyperdynamic circulation and vasoconstriction of renal circulation.
2. Stimulation of renal sympathetic nervous system
3. Increase of renal humoral synthesis and vasoactive mediator

The diagnosis of HRS using the International Ascites Club's diagnostic criteria of Hepatorenal Syndrome, consists of major criteria and additional criteria as presented in table below[12].

Table 4. International Ascites Club Diagnostic Criteria for Hepatorenal Syndrome

Major Criteria	Additional Criteria
Acute of chronic liver disease with advanced hepatic failure and portal hypertension.	1. Urine volume < 500ml / day
Low GFR, indicated by serum creatinine >1,5 mg/dl (130 µmol/L) or clearance creatinine in 24H < 40 ml/min.	2. Urine sodium < 10 meq/L
Exclusion of shock, ongoing bacterial infection, volume depletion, and the use of any nephrotoxic drug.	3. Urine osmolality > plasma osmolality
No improvement in renal function after given 1.5 L expander plasma and diuretic (decrease in serum creatinine <1.5 mg/dl or increase clearance creatinine >40 ml/min).	4. Urine red blood celss < 50 / high power field
Proteinuria < 0,5 g/day with no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.	5. Serum sodium concentration < 130 mEq/L
*Only major criteria are necessary for the diagnosis of hepatorenal syndrome.	

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is protein produced by distal nephron (thick ascending limb of Henle's loop, distal tubules, and collectives tubules), bound to the gelatinase from neutrophil cells.[13] The NGAL protein has anti-bacterial role, which help renal epithelial cells growth and differentiation. If renal tubules are damaged, NGAL level will increase to induced re-epithelialization of the tubules. This mechanism explains the increased level of NGAL in acute kidney injury.[14,15,16]

Acute kidney injury (AKI) on cirrhotic patients will worsen the prognosis. Research found that NGAL could differentiate types of AKI that occurs in cirrhotic patients. Several form of AKI that occur in patients with cirrhosis are prerenal azotemia, hepatorenal syndrome, and acute tubular necrosis. This research will study hepatorenal syndrome occurrence in HC patients.

METHOD

Study design

This study used a cross-sectional design which aims to determine the differences of urinary NGAL level in liver cirrhosis patients. Dependent variables in this study were cirrhotic patients with and without hepatorenal syndrome. Independent variables were urinary NGAL level.

Study Subject

Subject of this research were HC patients with hepatorenal syndrome who came to RSUP H. Adam Malik and USU Network Hospital. Sample of this study was taken by consecutive sampling, where subjects who came and met the inclusion criteria were included in the study. Patients under 18 years old, history of systemic disease, sepsis and malignancy, previous history of renal disease, AKI caused by other except HRS, and subject who refused to be part of this study are excluded. With a 95% confidence level, 20 subject are needed in each HC group, with and without HRS, with a total of 40 subject as minimum sample number required.

Study Method

Cirrhotic patients with and without HRS, who came to RSUP H. Adam Malik and USU Networking Hospital, and matched the inclusion criteria were asked to sign informed consent before included in this research. To diagnose hepatorenal syndrome based on International Ascites Club's criteria, patients will undergo history taking followed by renal function test and renal ultrasonography. Samples that meet the criteria will be taken for urinary NGAL test with ELISA method, both patients group: with and without hepatorenal syndrome. Data will be analysed after all laboratory tests are done.

Statistical Analysis

Demographic data was analysed using univariate analysis. Bivariate analysis was used to differentiate urinary NGAL level in both cirrhotic group, with and without HRS. T-Independent test was used in samples that were normally distributed, or Mann-Whitney test if samples were not normally distributed. P value<0,005 showed result was statistically significant.

RESULT

Sample characteristics

Table 5. The demographic characteristic of study respondents

Characteristic	n = 46
Gender	
Male	27(58,7%)
Female	19 (41,3%)
Age (years), mean ± SD	55,96 ± 8,66
Body weight (kg), mean ± SD	60,22 ± 5,95
Child-Pugh Classification	
A	1 (2,2%)
B	21 (45,7%)
C	24 (52,2%)
Cirrhosis Etiology	
Hepatitis B	28 (60,9%)
Hepatitis C	1 (2,2%)
Others	17 (37%)

There were 46 respondents with liver cirrhosis participated in this research. 26 out of 46 respondents were present with hepatorenal syndrome while 20 others were present without hepatorenal syndrome. Table 5 shows the demographic characteristic of the respondent. There were 27 male respondents (58.7%) and 19 female respondents (41.3%) with average age of 55.96 years and average body weight of 60.22 kg. The majority of liver cirrhosis in this study were caused by hepatitis B virus as many as 28 people (60.9%). The severity of cirrhosis was grouped based on Child-Pugh classification with 52.2% (24 respondents) were classified as C group with decompensated liver disease.

Etiology and HRS Complication

Table 6 describe the presence of hepatorenal syndrome (HRS) among respondent. There were 16 male respondents with HRS and 11 male respondents without HRS. The mean age in the HC without HRS group was 53.95 years and in the hepatic cirrhosis with HRS group was 57.50 years.

Hepatitis B infection was the most common cause of cirrhosis in HC patient with (53,8%) and without HRS (70%) participated in this study. The participant in this study was grouped based on the Child-Pugh classification. Seventeen participants (65,4%) with HRS were classified to the group C of the Child-Pugh classification. While in the participant group presenting without HRS 12 participants (60%) were classified into group B of the Child-Pugh classification.

Table 6. Sample distribution based on etiology and complication.

Characteristics	Liver Cirrhosis	
	Without HRS n = 20	With HRS n = 26
Gender		
Male	11 (55%)	16 (61,5%)
Female	9 (45%)	10 (38,5%)
Age (years), mean ± SD	53,95 ± 8,10	57,50 ± 8,91
Body weight (kg), mean ± SD	61,75 ± 5,68	59,04 ± 5,9
Child-Pugh classification		
A	1 (5%)	0 (0%)
B	12 (60%)	9 (34,6%)
C	7 (35%)	17 (65,4%)
Etiology		
Hepatitis B	14 (70%)	14 (53,8%)
Hepatitis C	0 (0%)	1 (3,8%)
Others	6 (30%)	11 (42,3%)

Laboratory Characteristic

Table 7 showed the distribution of laboratory value in hepatic cirrhosis (HC) patient with and without HRS. In HC patients without HRS group the mean haemoglobin was 10,11 gr/dL, mean

leukocyte count was 6.550/µL, mean platelet count was 137.400/µL, mean natrium level was 130,5 mEq/L, mean potassium level was 4,02 mEq/L, mean chloride level was 99,1 mEq/L, mean ureum was 34,95 mg/dL, mean creatinine was 0,77 mg/dL, mean albumin was 2,39 g/dL, mean bilirubin was 4,99 mg/dL, mean SGOT was 72,30 U/L, mean SGPT was 40 U/L, mean INR was 1,65.

Table 7. Laboratory characteristic of Study Respondents.

Laboratory	HC wihout HRS (n=20)	HC with HRS (n=26)	*p* value
Hemoglobim	9.65 (5.8-15.8)	8.95 (7.5-12.2)	0.191
leukocyte	6550 ± 2695.954	8128.08 ± 2935.012	0.068
Platelets	137400.00 ± 68552.247	135576.92 ± 48005.144	0.916
Natrium	130.50 ± 7.023	130.81 ± 8.159	0.894
Potassium	4.025 ± 0.9369	4.472 ± 0.9988	0.129
Chloride	101.00 (87-107)	101.50 (75-107)	0.697
Ureum	25.00 (15-98)	88.5 (28-137)	0.000*
Creatinine	0.735 (0.43-1.38)	2.485 (1.54-3.70)	0.000*
LFG	95.5 (47-146)	26.50 (14-56)	0.000*
Albumin	2.35 (1.7-3.2)	2.50 (1.7-4.4)	0.143
Total Bilirubin	2.65 (0.7-25)	3.10 (0.5-25.5)	0.790
SGOT	48.00 (11-244)	83.50 (13-128)	0.071
SGPT	35.00 (10-131)	51.50 (18-196)	0.050
INR	1.53 (0.98-3.45)	1.40 (0.92-2.50)	0.444

In the HC patients with HRS group the mean haemoglobin level was 9,5 gr/dL, mean leukocyte count was 8128/µL, mean platelet count was 135.576/µL, mean natrium level was 130,81 mEq/L, mean potassium level was 4,47 mEq/L, mean chloride level was 98,73 mEq/L, mean ureum was 132,12 mg/dL, mean creatinine was 2,45 mg/dL, mean albumin was 2,66 g/dL, mean bilirubin was 5,89 mg/dL, mean SGOT was 110,96 U/L, mean SGPT was 66,85 U/L, and mean INR was 1,54.

Urinary NGAL Level in HC patients with and without HRS

The mean urinary NGAL level in HC patient without HRS was 59.38 ± 58.98 ng/ml, while the mean urinary NGAL level in HC patient presenting with HRS was 130.78 ± 45.14 ng/ml. Independent T test was done with *p* value 0.000 that shows significant difference in urinary NGAL level in HC patient presenting with and without HRS.

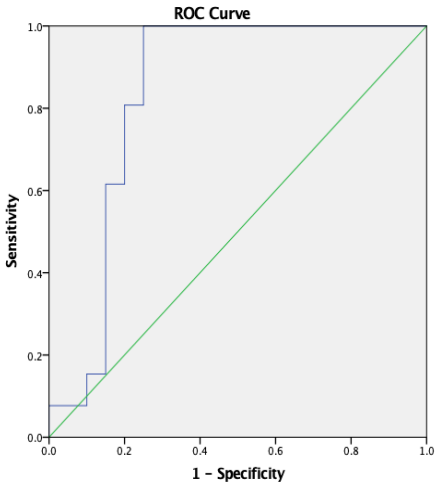
Table 8. Urinary NGAL level in HC patient with and without HRS.

	SHR	SH	*P* value
Urinary NGAL	130.78 ± 45.14	59.38 ± 58.98	0.000

Urinary NGAL cutoff to differentiate HC with and without HRS obtained in this study was 95,115 ng/ml, with *area under curve* (AUC) 0,837 (sensitivity 80,8%, specificity 75%, PPV 80,76%, and NPV 75%).

Table 9. Sensitivity, specificity, PPV, and NPV urinary NGAL level in HC patient with HRS.

	Cut off	AUC	Sensitivity	Specificty	PPV	NPV
NGAL Urine (ng/mL)	95.115	0.837	80.8%	75%	80.76%	75%



Picture 1. ROC Curve for urinary NGAL in HC patient with HRS

DISCUSSION

The aim of this study was to detect the level of urinary NGAL in cirrhosis patient presenting with and without HRS. 46 patients with hepatic cirrhosis were included in this study. Based on table 4.2, HRS were mostly found within male group (68.5%) while the prevalence of HRS within female group was 38.5%. The same result was reported by Hamdy et al. that HRS were predominantly found in men than women (58.6% vs 41.4%).[17]

The mean age in this study was 53.95 ± 8.10 years in HC without HRS and 57.35 ± 8.91 years in HC with HRS. These results are not much different from the study

conducted by Verna et al that reports the mean age of HC patients with HRS was 57 years (54.5–64.5) and 54.5 years (46–60.5) in HC patients without HRS. El Bassat et al reported the mean age of CH patients with HRS was 56 ± 10 years.[18,19]

The most common etiology of CH in this study was Hepatitis B virus (60.9%). Most patients (52.2%) included in this study were classified into group C of Child-Pugh classification. The same result was found in the study conducted in Turket by Gungor et al that shows the most common etiology of CH was Hepatitis B infection. However, different result was obtained by by Verna et al and El Bassat et al which found that the most common cause of HC was hepatitis C virus with percentage 45% and 94% respectively.[18,19,20]

The difference in CH etiology was because the difference in hepatitis virus prevalence worldwide. The 2013 RISKESDAS stated that the prevalence of people infected by hepatitis virus in Indonesia was 1.2%, this number was twice higher than in 2007. The most common types of hepatitis virus that was found within the population were hepatitis B (21.8%), hepatitis A (19.3%) and hepatitis C (2.5%). Indonesia is a country with high endemicity of Hepatitis B infection, the second largest in Southeast Asia after Myanmar. Based on WHO data, the highest prevalence of hepatitis C virus infection in 2015 was found in the Middle East-Mediterranean Region and Europe with prevalence rates of 2.3% and 1.5%, respectively, while the prevalence of hepatitis C virus infection outside those region varied from 0.5% to 1%.[21,22]

This study found there was a significant difference in urine NGAL level between HC patients with and without HRS. The mean urine NGAL level in HC patient without HRS in this study was 59.39 ± 58.98 ng/ml, while the average urine NGAL level in HC patient presenting with HRS was 130.78 ± 45.14 ng/ml with *p* value 0.000 that shows there was difference in urinary NGAL level found in HC patient presenting with and without HRS. The result found in his study was in accordance with the study conducted by Verna et al that shows higher urinary NGAL level in HC patient with HRS (105 (27.5–387.5) vs 20 (10–47.5); $p = 0.001$). Similar result was concluded in the study conducted by Fagundez et al (76 (43–263) vs 40 (25–82)). In another study, El Bassat et al shows that urinary NGAL level in HC with HRS were significantly higher than HC without HRS (105 ± 30.5 vs. 31 ± 12.3; P = 0.001).[18,19,23]

In this study, the cutoff of urinary NGAL level to differentiate HC with HRS and HC without HRS was 95.115 ng/ml, with area under curve (AUC) 0.88 (sensitivity 84.6%, specificity 92.3%, PPV 91.6%, and NPV 85,7%). In the research conducted by El-Bassat et al found that the cutoff value for diagnosing HRS was 110 ng/ml (sensitivity 90.2%; specificity 67.9%; PPV 79%; NPV 91%). In another research conducted by Verna et al obtained a cutoff level of 110 ng/ml to differentiate pre-renal and non-pre-renal AKI in cirrhotic patients (88% sensitivity; 85% specificity). According to a study conducted by Hamdy et al., urinary NGAL level > 143 ng/ml can differentiate ATN from HRS in cirrhotic patients with an AUC of 0.822 (75% sensitivity; 80% specificity; PPV 84.3%; NPV 69.1%).[17, 19]

CONCLUSION

This study concluded that higher urinary NGAL level was found within HC patient presenting with HRS than HC patient without HRS (*p* value = 0.000) with urinary NGAL level cutoff level was 95,115 ng/ml. A multicentered follow up study with larger sample were needed to further support the results of this study.

Acknowledgement: None

Conflict of Interest: None

Source of Funding: None

Ethical Approval: Approved

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How to cite this article: Fakhrurrazi Nasution, Gontar Alamsyah Siregar, Ilhamd et.al. The difference of urinary neutrophil gelatinase-associated lipocalin level between liver cirrhosis patients with and without hepatorenal syndrome. *International Journal of Research and Review*. 2022; 9(1): 1-8. DOI: *https://doi.org/10.52403/ijrr.20220101*

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