Red cell distribution width to lymphocyte ratio as a new biomarker in predicting prognosis in chronic liver disease patients with hepatocellular carcinoma

Yakup Ülger*; Anıl Delik

Faculty of Medicine, Department of Gastroenterology, Çukurova University, Adana 01330, Turkey.

*Corresponding Author: Yakup Ülger

Çukurova University, Faculty of Medicine, Department of Gastroenterology, Adana, Turkey.

Tel: 0322-338-60-60; Email: yakup73us@yahoo.com

Abstract

Background: Hepatocellular Carcinoma (HCC), hepatitis B, hepatitis C, chronic alcoholism, non-alcoholic fatty liver disease, copper and iron deposition etiologies, together with various genetic factors, constitute a rather complex cancer group that includes chronic inflammation, chronic systemic inflammation triggered by oxidative stress. Therefore, an increase in the incidence and prevalence of liver cancer is expected in the future. Discovery of new biomarkers in HCC diagnosis, prognosis, prediction of treatment response and treatment follow-up is very important. The aim of our study was to retrospectively evaluate the clinical significance of the Red blood cell Distribution Width (RDW) to lymphocyte ratio (RLR) in patients with chronic liver disease with HCC.

Materials and methods: Our study, which was designed retrospectively, included 200 patients who were followed up with the diagnosis of HCC. Liver function tests, hematological parameters, biochemical tests were analyzed in Çukurova University Balcalı hospital. Child Pugh Score (CTP) and RLR of the patients were calculated with the necessary equations. HCC patients were analyzed in two groups as alfa feto protein (AFP) negative (<20 ng/ml) and AFP positive (>20 ng/ml). All the obtained results were analyzed in SPSS program.

Results: A total of 200 patients with HCC were included in this study. Half of the 200 HCC patients included in the study were found to be AFP negative, and the gender distribution in this group was found to be 24.2% for women and 75.8% for men. A significant increase in the rate of RLR was detected in the AFP positive group (AFP negative 13.54 ± 9.67, AFP positive 20.11 ± 27.38, and p value 0.03). According to Child Pugh score, RLR rates were found to be 11.72 ± 8.82 in CTP A, 15.96 ± 8.78 in CTP B, 27.47 ± 35.6 in CTP C, p value <0.001. In multivariate logistic regression analysis according to AFP group distribution, the OR value of RLR was determined as 0.95, 95% CI (0.90-1.00) and p value was 0.02.

Conclusion: We think that RLR can be used as a new biomarker associated with poor prognosis in AFP positive HCC patients.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common and aggressive malignancies of the liver [1]. It is the 4th leading cause of cancer-related death in the worldwide [2]. Chronic hepatitises (such as hepatitis B virus (HBV), Hepatitis C virus (HCV), chronic alcohol consumption, non-alcoholic steatohepatitis are the main risk factors for HCC [3].

Various classifications are used to predict the prognosis and evaluate liver functional reserve in HCC patients such as Child-Pugh (CTP) score, model for end-stage liver disease (MELD) score, Barcellona clinic liver cancer (BCLC) score [4]. HCC often develops in the background of chronic liver disease. liver biopsy still remains the gold standard in the diagnosis of cirrhosis, despite its negative aspects such as being an invasive method, risk of complications, sampling errors, and different evaluations by different pathologists [5,6]. Recently, laboratory parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-monocytes ratio (NMR) have been used to evaluate liver function, risk of liver failure after hepatectomy, and survival in HCC patients [7-11]. The goal of this study is to evaluate the role of RLR level in clinical practice as an important biomarker in predicting prognosis in HCC patients.

Materials and methods

Study population

The medical records of the patients who were followed up with the diagnosis of HCC in our department between January 2010 and June 2020 were retrospectively reviewed. Exclusion criteria were: mixed hepatocellular cholangiocarcinoma; missing information about its calculation; and co-existing hematological disease. Our study was in accordance with the Declaration of Helsinki [12] and was approved by the Çukurova Medical Faculty Balcalı Hospital Ethics Committee. Written informed consent was obtained from the patients. The HCC diagnostic criteria were based on the guidelines recommended by the European Association for the Study of the Liver (EASL) [13]. We diagnosed HCC when a patient had one or more risk factors: examination using α-fetoprotein (AFP) and spiral computed tomography (CT), dynamic MRI with contrast; or AFP and at least two findings following CT, MRI. A positive HCC finding using dynamic CT or MRI is indicative of venous clearance after arterial increase in the delayed portal/venous phase. In addition, we made a histopathological diagnosis in cases that did not meet all clinical noninvasive diagnostic criteria for HCC.

Statistical analysis

We used SPSS version 18.0 for data entry and analysis. Normally distributed continuous variables (Kolmogorov–Smirnov test, $P > .05$) were expressed as mean value ± standard deviation (SD). Or the median (interquartile range) was used. Comparisons between groups were made using the t, Wilcoxon or χ^2 test, as appropriate. Data divided into two groups showing parametric distribution were evaluated with the Anova test, and the data with non-parametric distribution analyzed in three groups were evaluated with the Kruskal Wallis test. P value $<.05$ was considered statistically significant.

Results

A total of 200 patients were included in the study. 77.9% of the patients were male and 22.1% were female. The mean age of HCC patients was 64.79 ± 11.41 years. The patients were evaluated in two groups as AFP negative (50%) and AFP positive (50%). AST level 91.54 ± 216 in AFP negative group, 266.13 ± 1301 p value 0.001 in AFP positive group, GGT level 109 ± 150, 140 ± 144, p value 0.006, ALP level 167 ± 298, 196 ± 173, p value 0.001, CRP level 4.42 ± 6.71, 9.74 ± 16.54, p value 0.01, ferritin level 205 ± 498, 397 ± 766, p value 0.01, RLR level 13.54 ± 54, 20.11 ± 27.38, p value 0.03. Other demographic results are shown in (Table 1).

Table 1: Demographic data by alpha feto protein distribution in hepatocellular carcinoma patients.

Variable	AFP negative (n=100)	AFP positive (n=100)	P value
Gender (n,%)			0.18
Female	23 (24.2)	18 (18)	
Male	72 (75.8)	82 (82)	
Age, (yr)	64.93 ± 10.43	64.57 ± 12.56	0.82
HGB, gr/dl	12.62 ± 2.47	12.65 ± 2.53	0.93
Glucose, mg/dl	119 ± 46	129 ± 73	0.85
Creatinin, mg/dl	1.12 ± 0.95	2.06 ± 8.05	0.28
ALT, U/L	62.62 ± 83	124.85 ± 606	0.06
AST, U/L	91.54 ± 216	266.13 ± 1301	0.001
GGT, U/L	109 ± 150	140 ± 144	0.006
ALB, g/L	3.24 ± 0.7	3.29 ± 4.2	0.90
ALP, U/L	167 ± 298	196 ± 173	0.001
T.BİL, mg/dl	3.94 ± 9.6	3.62 ± 5.4	0.77
D.BİL, mg/dl	1.54 ± 3.4	3 ± 8.6	0.14
Calcium, mg/dl	9.20 ± 0.9	9.48 ± 1.3	0.16
PT	14.84 ± 4.18	15.69 ± 7.32	0.32
INR	1.26 ± 0.24	2.79 ± 13.8	0.29
CRP, mg/dl	4.42 ± 6.71	9.74 ± 16.54	0.01
Ferritin, ng/ml	205 ± 498	397 ± 766	0.01
Child pugh (n,%)			0.41
Child A	28 (43.8)	29 (34.9)	
Child B	19 (29.7)	24 (28.9)	
Child C	17 (26.6)	30 (36.1)	
RLR	13.54 ± 9.67	20.11 ± 27.38	0.03

HGB: Hemoglobine; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase; ALB: Albumine; ALP: Alkaline phosphatase; T.BİL: Total Bilirubin; D.BIL: Direct Bilirubin; PT: Prothrombin Time; INR: International Normalized Ratio; CRP: C-reactive protein; RLR: Red cell distribution width to lymphocyte ratio.

Distribution of HCC patients by child pugh score, RLR level 11.72 ± 8.82 in Child A group, 15.96 ± 8.78 in Child B group, 27.47 ± 35.6 in Child C group, p value <0.001, CRP level 5.15 ± 14 in Child A group, 6.14± in Child B group 7.88, 12.90 ± 16.99 in Child C group, p value <0.001, ferritin level 183 ± 369 in Child A group, 144 ± 140 in Child B group, 652 ± 1000 in Child C group, p value 0.001. All demographic data according to Child Pugh score are given in (Table 2).

According to logistic regression analysis according to AFP distribution in HCC patients, RLR level OR 0.95 95 %CI (0.9-1.00), p value 0.02, CRP level OR 0.93, 95 %CI (0.87-1.00), p value 0.02, ALP level OR 1.00, 95 %CI (0.99-1.00), p value was determined as 0.07. All of the logistic regression analysis results are given in (Table 3).

Table 2: Distribution of data by Child Pugh score in hepatocellular carcinoma patients.

Variable	Child A	Child B	Child C	P value
RLR	11.72 ± 8.82	15.96 ± 8.78	27.47 ± 35.6	<0.001
ALT, U/L	40 ± 29	193 ± 922	94 ± 140	<0.001
AST, U/L	51 ± 40	392 ± 196	222 ± 332	<0.001
GGT, U/L	103 ± 104	109 ± 108	181 ± 204	0.09
ALP, U/L	117 ± 79	163 ± 115	340 ± 433	<0.001
CRP, mg/dl	5.15 ± 14	6.14 ± 7.88	12.90 ± 16.99	<0.001
Ferritin, ng/ml	183 ± 369	144 ± 140	652 ± 1000	<0.001
ALB, g/L	4.18 ± 5.47	2.89 ± 0.60	2.38 ± 0.59	<0.001

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase ALB: Albumine; ALP: Alkaline Phosphatase; CRP: C-Reactive Protein; RLR: Red Cell Distribution Width To Lymphocyte Ratio.

Table 3: Logistic regression analysis according to AFP distribution in hepatocellular carcinoma patients.

Variable	O.R	95 %CI Lower	95 %CI Upper	P value
Age, (yr)	1.03	0.98	1.07	0.13
ALT, U/L	1.00	0.99	1.00	0.89
AST, U/L	1.00	0.99	1.00	0.86
GGT, U/L	0.99	0.99	1.00	0.18
ALP, U/L	1.00	0.99	1.00	0.07
CRP, mg/dl	0.93	0.87	1.00	0.02
Ferritin, ng/ml	1.00	0.99	1.00	0.74
RLR	0.95	0.90	1.00	0.02

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase; ALP: Alkaline Phosphatase; CRP: C-Reactive Protein; RLR: Red Cell Distribution Width To Lymphocyte Ratio.

Discussion

RDW is a noninvasive, routinely measured hematological parameter that reflects anisocytosis. Recently, it has been reported that RDW may be a prognostic biomarker in predicting the clinical course of various diseases such as cardiovascular diseases, sepsis, liver cirrhosis, autoimmune liver disease, cancers, leukemia, renal dysfunction and respiratory diseases [5,14-16]. S Jing, et al found the RDW level to be an optimal prognostic threshold of 14.15% in determining survival in HCC patients, and they found RDW level below this value to be associated with low mortality (p:<0.001) [17]. Some researchers have reported that the RLR (RDW to lymphocyte ratio) index is a good biomarker in predicting the severity of hepatic fibrosis and cirrhosis in NAFLD patients [18,19]. They showed that NAFLD patients had simple adiposity and higher RDW values compared to healthy individuals. It has been reported that increased RDW levels are positively correlated with severe hepatic fibrosis [20]. Wang et al reported that RLR and MPV (platelet volume) were associated with the severity of fibrosis in chronic hepatitis C patients. It is suggested that this will reduce the need for liver biopsy [21].

Zhang et al and Gao et al found that high RLR levels were associated with an increase in HBV-related cirrhosis and hepatitis b viral load [5,22]. On the contrary, Karagöz et al. found no significant relationship between these variables in patients undergoing liver transplantation [23].

In our study, in which the RLR index in HCC was evaluated for the first time in the Turkish population, it was shown that RLR is a biomarker associated with poor prognosis when the AFP negative HCC and AFP positive HCC groups are compared. (p:0.03). The limitations of this study were that it was small sample, single-center, and retrospective. RLR can be used as a biomarker to predict chronic liver disease severity and mortality in HCC patients.

Conclusion

We evaluate that RLR in AFP positive HCC is a simple, inexpensive and non-invasive new hematological biomarker useful in clinical practice in predicting prognosis.

Conflict of interest: The authors declare no conflict of interests

Author contributions: Conseption and design: YÜ, AD Collection and assembly of data: YU, AD Data analysis: YÜ manuscript writing: AD

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