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Is Neutrophil Lymphocyte Ratio a Useful Biomarker in Predicting Fibrosis in Chronic Hepatitis C Infection?

Yakup Ülger

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

ABSTRACT

Percutaneous liver biopsy is the gold standard in the evaluation of liver fibrosis in the chronic hepatitis C infection (HCV). Invasive biopsy leads to complication risks and high financial burden for each patient. Therefore, noninvasive methods are needed including neutrophil lymphocyte (NLR) ratio, thrombocyte lymphocyte ratio (PLR). The aim of this study was to investigate the effect of NLR and PLR as a biomarker on the prediction of response status and fibrosis degrees of patients with HCV.

Material and Methods: We enrolled 184 chronic HCV in patients this retrospective study. The NLR and PLR of the patients were calculated using the hemogram data in the hospital registry system. The patients were evaluated in two groups according to their antiviral treatment response, with sustained viral response (SVR) and no response (Non- SVR).

Results: It has been shown that SVR in HCV infection decreases with increasing age ($p = 0.04$). NLR was associated with the degree of fibrosis ($p=0.02$) while PLR was not significant ($p=0.21$). On the contrary, there was no significant relationship between NLR, PLR and treatment response status.

Conclusions: This study conducted in the Turkish population is the first study to reveal the relationship between response and fibrosis with NLR and PLR in chronic HCV infection using the largest sample size. Low NLR value can be used as a biomarker to predict advanced fibrosis due to chronic HCV.

Key Words: Chronic hepatitis C, Neutrophil-lymphocyte ratio, Platelet-lymphocyte ratio, liver fibrosis

Introduction

Chronic hepatitis C (HCV) infection is an important public health problem that causes chronic inflammatory necrosis, cirrhosis and hepatocellular carcinoma (HCC) in the worldwide (1). Percutaneous liver biopsy is the gold standard in the evaluation of liver fibrosis, but noninvasive methods are needed because of the invasive procedure, complication risks and costs (2). Noninvasive biomarkers such as neutrophil lymphocyte (NLR) ratio, thrombocyte lymphocyte ratio (PLR), aspartate aminotransferase thrombocyte ratio (APRI), fibrosis index based on the four factors (FIB-4) score are used to predict fibrosis in patients with chronic liver disease (3,4). NLR is widely used as a biomarker to evaluate prognosis in various cancer patients such as; overian, colorectal, breast, pancreatic, renal cell cancers, glioma, myeloma (5-10). Increased neutrophil levels are associated with chronic inflammation, while decreased lymphocyte levels are associated with bacterial infection (11). Systematic inflammation has a recognized role in the pathogenesis of advanced cirrhosis. Necroinflammation is one of the features of liver disease, especially in advanced cirrhosis. The NLR may be a marker to show the severity of hepatocellular damage in progressive fibrosis. Both NLR and Child-Turcotte-Pugh (CTP) can be used to independently predict poor outcome (12,13). NLR has been shown to be higher in patients with decompensated cirrhosis than compensated cirrhosis (14). The aim of this study was to investigate the effect of NLR and PLR as a marker on the prediction of response status and fibrosis degrees of patients with HCV.

Materials and Metods

In our study, 184 patients with chronic HCV infection with genotype 1 who received pegylated interferon (PEG-IFN) plus ribavirin (RBV) treatment between January 2007 and June 2011 at Çukurova University Balcalı Hospital were included. Approved by the Ethics Committee. Informed consent of the patients was obtained. The diagnosis of chronic HCV infection was defined in the presence of anti-HCV antibody, HCV RNA positivity, continuous increase in alanine aminotransferase (ALT) for at least six months, clinical and histological findings. Gamma glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), triglyceride (TG), platelet

*Corresponding Author: Dr. Yakup Ülger, Department of Gastroenterology, Faculty of Medicine, Çukurova University, Adana, Turkey
E-mail: yakup73us@yahoo.com, Phone: 0(506) 437 99 57
ORCID ID: Yakup Ülger: 0000-0003-2999-9308
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Table 1. Distribution of selected characteristics in SVR and non-SVR

Variable	SVR, (N=134)	non-SVR, (N=50)	P value
Male, (%)	60 (38.8)	18 (36)	0.73
Age	55.2±13.2	59.9±13.3	0.04
BMI (kg/m2)	24.1±3.4	23.8 ±3.7	0.56
HCV RNA log(IU/ml)	6.25(2.61-7.71)	6.49(4.95-6.85)	0.45
Fibrosis 0-2/3-4 (%)	35/57 (38/62)	6/26 (19/81)	0.04
Neutrophil/Lymphocyte	1.94 (0.75-7.25)	1.93 (0.55-4.75)	0.92
Platelet/Lymphocyte	113.7 (18-427.8)	106.4 (13.5-404.2)	0.44
Albumin (g/dL)	3.90 ± 0.46	3.65 ± 0.71	0.007
Triglyceride(mg/dl)	115 (27-332)	82 (36-286)	0.01
Total cholesterol (mg/dl)	170 (68-327)	146 (76-225)	0.003
LDL (mg/dl)	100 (27-262)	83.5 (27-149)	0.001
HDL (mg/dl)	40 (14-97)	44.53 (11-103)	0.23
AST (U/L)	30.5 (11-188)	45 (16-122)	0.0001
ALT (U/L)	18 (5-209)	39 (17-235)	0.002
GGT (U/L)	23 (7-543)	32.5 (7-277)	0.02
ALP (U/L)	74.5 (32-382)	81.5 (5-366)	0.12
HCT (%)	39.14 ± 5.66	39.47 ± 6.64	0.74
HGB (g/dl)	12.99 ± 1.88	13.03 ± 2.25	0.91
WBC,x109/l	6.44 (1.2-14.2)	6.12 (1.0-14.5)	0.11
Neutrophil, x109/l	3.60 (0.60-9.10)	3.13 (0.48-9.50)	0.04
Lymphocyte, x109/l	1.90 (0.3-4.60)	1.71 (0.37-3.64)	0.12
Platelet, x109/l	235 (14-415)	184.5 (5-442)	0.006

HCV RNA, alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), triglyceride (TG), counts of platelet (PLT), neutrophil, lymphocyte and hematocrit (HCT)

(PLT), neutrophil, lymphocyte counts and hematocrit (HCT) levels were statistically analyzed.

Exclusion Criteria: Patients with co-infection (HBV, HIV), autoimmune hepatitis, alcoholic hepatitis, HCC, other hematological and malignant diseases, and drug use affecting platelet count were excluded from the study.

Data Collection: The pre-treatment blood values of 184 HCV patients in the hospital were analyzed. The degree of fibrosis was categorized as F0-2 and F3-4, Metavır score. Moreover, NLR and PLR was calculated by dividing the absolute neutrophil and platelet count by the absolute lymphocyte count, respectively.

Statistical Analysis: Data was analyzed using the computer software IBM Statistical Package for Social Sciences for Windows. Continues variables are showed as the mean (standard deviation, SD) or median (min-max) for abnormal distributions and categorical data are submitted as frequencies (%). Comparisons in the distributions of demographical characteristics between the responders and the non-responders were analyzed using the Student's t-test or Mann-Whitney U test for continuous variables, and chi-square test for categorical variables. All tests were two-sided and P value <0.05 was accepted significant.

Results

The clinical and demographic characteristics of the 184 patients are shown Table 1. 72.8% of the patients (n=134) were categorized as sustained virological response group (SVR) and 27.2% (n=50) were classified as non-sustained virological response group (non-SVR), all of whom were Turkish and Caucasians. A majority of both groups were female. There were significant differences between the both groups as regards ALT, AST, GGT, LDL, albumin, TG, PLT, neutrophil levels and fibrosis degrees. Moreover, the response status has been associated with degree of fibrosis. No significant association was found with NLR and PLR treatment response status (Table 1).

But, NLR was associated with the degree of fibrosis while PLR was not significant. Moreover, The association between degree of fibrosis and AST, GGT, PLT, neutrophil, HGB, TG levels were found to be significant (Table 2). While there is no

Table 2. Data of Patients According to Fibrosis Degree

Variable	F0-2, N=41	F3-4, N=83	P value
Male, (%)	%39	%33.7	0.56
Age	47.98 ± 14.96	58.88 ± 10.31	0.001
HCV RNA log(IU/ml)	6.09 (4.21-6.87)	6.13 (2.61-6.55)	0.88
Neutrophil/Lymphocyte	2.17 (0.55-7.25)	1.78 (0.75-5.44)	0.02
Platelet/Lymphocyte	114.1 (35.6-276.3)	105 (13.5-404.2)	0.21
Albumin (g/dL)	3.97 ± 0.53	3.85 ± 0.49	0.25
Triglyceride(mg/dl)	136 (35-332)	98 (27-287)	0.01
Total cholesterol (mg/dl)	161 (80-289)	160 (76-327)	0.37
LDL (mg/dl)	96 (27-262)	95 (30-248)	0.54
HDL (mg/dl)	40.8 (11-93)	40 (15-83)	0.66
AST (U/L)	26 (12-122)	35 (11-105)	0.08
ALT (U/L)	27 (12-139)	28 (5-164)	0.55
GGT (U/L)	22 (8-111)	29 (9-543)	0.02
ALP (U/L)	72 (32-243)	84 (33-382)	0.22
HCT (%)	40.70 ± 5.86	38.87 ± 5.92	0.11
HGB (g/dl)	13.63 ± 1.99	12.93 ± 2.00	0.05
WBC,x109/l	6.74 (3.2-14.5)	6.11 (1-10.7)	0.01
Neutrophil, x109/l	4.05 (1.80-9.50)	3.20 (0.48-6.80)	0.0001
Lymphocyte, x109/l	2.1 (0.7-4.6)	1.86 (0.3-3.8)	.012
Platelet, x109/l	239 (81-393)	199 (5-367)	0.002

HCV RNA, alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), triglyceride (TG), counts of platelet (PLT), neutrophil, lymphocyte and hematocrit (HCT)

statistically significant relationship between antiviral treatment response and viral load in chronic hepatitis C (p= 0.45). it has been shown that treatment response decreases with increasing age (p=0.04).

Discussion

HCV infection leads to the development of chronic hepatitis, cirrhosis, acute liver failure and liver cancer. Early diagnosis and evaluation of liver fibrosis plays a crucial role in controlling disease progression and therapeutic approach for these patients. Although liver biopsy is the gold standard in evaluating fibrosis, it has disadvantages such as invasiveness, complications, cost, and the tissue sample taken does not represent the whole liver. For these reasons, non-invasive models should be created to determine liver fibrosis. NLR and PLR have been associated with systemic inflammation and poor prognosis in various cancers (15-17). There was no difference in NLR values in the differentiation of mild fibrosis (F1-F2), severe fibrosis (F3-F6 according to Ishak score) and cirrhosis in patients with HCV-related liver disease (18,19). While studies by Meng et al and Çoşkun et al. supported these findings (1,19), on the contrary, Abdel-Razik et al found the NLR value to be high in advanced stage liver disease (20). It is reported that NLR is lower in advanced stage fibrosis due to chronic hepatitis B (21,22), but there are studies showing that NLR is higher in advanced fibrosis (F3-F4) (20). Alkhouri et al. Reported higher NLR values in NASH and advanced fibrosis (20). Meng et al. have shown that PLR in chronic HCV is associated with the severity of hepatocellular damage and response to treatment compared to NLR (1). Significant fibrosis due to chronic HCV was found to be associated with mean platelet volume by Kuzu et al, But no relationship was found with NLR (23). Çoskun et al. found that there was no relationship between NLR and liver histological activity index (according to the ishak score) in patients with chronic HCV, and the NLR value was lower in the presence of advanced fibrosis and cirrhosis (19).

Results of the limited number of studies are controversial. In order to enlighten this issue in HCV, it is necessary to study with a larger number of patients and to make meta-analysis. Our study is the first study in the Turkish population, which includes the large sample size in chronic HCV, in which the treatment response relationship with NLR and PLR was investigated. While there is no significant relationship between sustained response and NLR and PLR, the response status is associated with fibrosis. NLR was associated with the degree of

fibrosis while PLR was not significant. A statistically significant relationship was found between response status and neutrophil, platelet, ALT, AST, GGT, Total cholesterol, LDL, triglyceride levels. The degree of fibrosis and AST, GGT, PLT, Neutrophil, HGB, TG levels were found to be significant. Results of the limited number of studies are controversial. In order to enlighten this issue in HCV, it is necessary to study with a larger number of patients and to make meta-analysis.

In conclusion, this study conducted in the Turkish population is the first study to reveal the relationship between response and fibrosis with NLR and PLR in chronic HCV infection using the largest sample size. While NLR was associated with the degree of fibrosis, PLR was not found to be significant. No significant correlation was found with NLR and PLR according to response status. Low NLR value can be used as a biomarker to predict advanced fibrosis due to chronic HCV.

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