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The platelet-to-lymphocyte ratio, superior to the neutrophil-to-lymphocyte ratio, correlates with hepatitis C virus infection

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SUMMARY

Objectives: The platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) have been studied widely in cancer diseases. However, their correlation with hepatitis C virus (HCV) infection is unknown. The aim of this study was to investigate the correlation of PLR and NLR with disease severity in patients with HCV-related liver disease and the virological response in chronic hepatitis C (CHC) patients.

Methods: The clinical data of 120 HCV-infected patients and 40 healthy controls were analyzed. The clinical data of 24 CHC patients who had been followed up regularly were collected for the following time points: before treatment (week 0) and weeks 4, 48, and 72 during treatment. These data were also analyzed. All data were collected from the database of the hospital patient electronic medical record system.

Results: The HCV-related cirrhosis group and HCV-related hepatocellular carcinoma group were found to have lower PLRs (61 ± 31 and 51 ± 23) than the healthy controls (115 ± 23). The PLR of the HCV cleared group (154 ± 85) was significantly higher than that of the HCV untreated group and HCV uncleared group (90 ± 28 and 88 ± 40, respectively). Receiver operating characteristics curve analysis for the PLR showed an area under the curve of 0.772 (95% confidence interval 0.674–0.869, $p < 0.000$); for NLR, the area under the curve was 0.612 (95% confidence interval 0.495–0.730, $p = 0.063$). Furthermore, an increasing PLR in CHC patients indicated a good virological response, and a stable PLR or a downward trend in PLR could predict no rapid virological response being achieved by week 4, and even no sustained virological response by week 72.

Conclusions: The PLR is closely related to disease severity in patients with HCV-related liver disease and to the virological response in CHC patients. Dynamic continuous monitoring of the PLR will contribute to disease surveillance, with an increasing tendency predicting a good virological response.

1. Introduction

Chronic hepatitis C (CHC) is an inflammatory liver disease caused by the hepatitis C virus (HCV), which is a major public health problem and a leading cause of chronic liver disease. With its characteristic high degree of chronicity, HCV infection often causes chronic inflammatory necrosis of the liver, which leads to liver cirrhosis and even hepatocellular carcinoma (HCC).[1] It is estimated that there are nearly 185 million people infected with HCV worldwide, with nearly 350 000 people dying each year from HCV infection-related liver disease. China is a high hepatitis C epidemic area with about 30 million infected persons, and is the country with the maximum number of infected cases in the world.[2]

With its high degree of chronicity, HCV infection is often associated with disorders of immune function. Studies have confirmed that cellular immunity plays an important role in the development of HCV infection, while a variety of cell factors are also involved.[3–5] Different subgroups of lymphocytes, like the effector T-cells (Teffs), regulatory T-cells (Tregs), and cytotoxic

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T-cells (CD8+ Tc), also play an important role in HCV infection.[6] Other indicators, such as proteins in the plasma, single nucleotide polymorphisms (SNPs) on chromosome 19 (rs12979860 and rs8099917) near the interleukin 28B (IL28B) region, and systemic levels of interferon gamma inducible protein 10 (IP-10), have been studied.[7,8] However, there is still no satisfactory index to indicate the progression of HCV-related liver disease or to monitor the antiviral response to treatment.

Recently, using advanced imaging technology, Guidotti et al. confirmed that by adhering to platelets in hepatic blood sinuses, intrahepatic CD8+ effector T-cells recognize and kill cancer cells, which can be damaged by the liver fibration.[9] Also, studies in liver cancer patients on the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), which are two important indicators of systemic inflammation and have been shown to be prognostic parameters in various cancer treatments,[10–12] have confirmed that these ratios are closely related to the progression and treatment outcomes of liver cancer.[13–16] Whether these two parameters are correlated with HCV infection, HCV-related liver cirrhosis, and HCC has not yet been established. The association of these two parameters with hepatitis disease progression and antiviral treatment outcomes, liver fibration, and cancerization also needs further research.

The aim of this study was to evaluate the clinical values of the NLR and PLR in HCV-infected patients in order to gain a better understanding of the role and significance of PLR and NLR in HCV infection-related liver disease. It was also sought to provide new indicator parameters for the clinical diagnosis of HCV infection and for HCV treatment.

2. Materials and methods

This study was reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Zhengzhou University. Due to the retrospective nature of the study, the need for informed consent was waived.

2.1. Patients

Following the application of inclusion and exclusion criteria, 120 HCV-infected patients and 40 healthy control subjects from the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China were included in the study from January 2013 to June 2015. Twenty-four CHC patients who had undergone regular follow-up for no less than 72 weeks were also included. The 120 patients were divided into different groups: 93 were assigned to the chronic HCV-related hepatitis group (HCV-Ht), including 31 in the HCV untreated group (HCV-UT), 41 in the HCV cleared group (HCV-Cl), and 21 in the HCV uncleared group (HCV-UC); 21 were assigned to the HCV-related cirrhosis group (HCV-Cirr) and six were assigned to the HCV-related HCC group (HCV-HCC). Cirrhosis and HCC were diagnosed according to clinic standards by laboratory parameters and liver histopathology tests.

With regard to the inclusion and exclusion criteria, patients with hepatitis B virus (HBV), HIV, or any other virus infection, autoimmune diseases such as systemic lupus erythematosus (SLE), potential immune-related diseases such as diabetes, leukemia or any other blood system diseases, or any other organic disease outside the liver were excluded. Patients receiving treatment with whole blood or any other component blood product transfusions were also excluded. In the HCV-Cl group, the patients' viral loads had been undetectable for at least 24 weeks. Patients in the HCV treated group were all receiving standard peg-interferon plus ribavirin antiviral therapy, and no serious adverse effects (anemia, neutropenia, thrombocytopenia, etc.) were caused by either interferon or ribavirin. Additionally, healthy controls were subjects without a history of any other infectious diseases or drug usage for the last 6 months. The inclusion and exclusion criteria were based on the clinical guidelines for HCV infection.[17,18]

2.2. Data collection

The following data were collected for all healthy control subjects and patients: age, sex, viral load (VL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), white blood cell count (WBC), platelet count (PLT), lymphocyte count, neutrophil count, and other related clinical indicators. For further analysis of the correlation of PLR and NLR with antiviral treatment outcomes, the clinical data of 24 CHC patients who had been followed up regularly were collected for the following time points: before treatment (week 0) and weeks 4, 48, and 72 during treatment.

2.3. Laboratory methods

All specimens were tested within 2 h of collection. Those that could not be tested immediately were stored at −20 °C for a short time (no more than 3 days). The HCV-RNA load was tested by fluorescence quantitative PCR method using the Cobas AmpliPrep/Cobas Taqman HCV Test and related reagents (Roche, Switzerland). A Cobas AmpliPrep device was used for fully automated sample preparation, and a Cobas Taqman analyzer was used for automatic amplification and detection of HCV-RNA. ALT and AST were detected by enzymatic method using a Cobas E702 automatic biochemical analyzer and related reagents (Roche), strictly in accordance with the instructions. The WBC, PLT, lymphocyte, and neutrophil counts were obtained based on the Coulter principle, using a Coulter LH 755 automated blood analyzer and related reagents (Beckman, USA), strictly in accordance with the instructions. The PLR and NLR were calculated as follows: PLR = platelet count/lymphocyte count;[19] NLR = neutrophil count/lymphocyte count.[20]

2.4. Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics version 21.0 software (IBM Corp., Armonk, NY, USA). Summary statistics of the study population were expressed as the mean ± standard deviation (mean ± SD) or median value with the interquartile range (IQR), as appropriate. The Kolmogorov–Smirnov test was performed to evaluate variable distribution. Comparisons of demographic and clinical parameters of the two groups were performed using the Chi-square test, Student *t*-test (independent samples *t*-test), or Mann–Whitney *U*-test, as appropriate; the Kruskal–Wallis test was used for the comparison of more than two groups. A receiver operating characteristic (ROC) curve was used for the evaluation of predictors and to determine their sensitivities and specificities. The Friedman test was used to compare the PLR and NLR of the different virological responders during antiviral treatment. All *p*-values of less than 0.05 based on a two-tailed test were considered statistically significant.

3. Results

3.1. General characteristics

A total of 120 HCV-infected patients and 40 healthy controls were included retrospectively in the present study. The characteristics of the participants in the two groups are summarized in Table 1. There was no significant difference in mean age or sex ratio between the patients and controls, while ALT and AST were considerably higher in patients than in controls (ALT 52 ± 55 vs.

Table 1
Demographic and clinical data for the different patient groups and healthy controls[a]

	HCV (groups)[b]					HCV (total)	Healthy controls	*p*-Value[c]
	HCV-UT	HCV-UC	HCV-Cl	HCV-Cirr	HCV-HCC			
n	31	21	41	21	6	120	40	NA
Sex, M/F	13/18	9/12	22/19	6/15	2/4	52/68	20/20	0.779
Age, years	42.4 ± 14.1	50.7 ± 9.2	42.2 ± 11.8	53.8 ± 7.4	59.0 ± 7.1	46.6 ± 12.4	45.6 ± 12.9	0.667
ALT, g/l	63 ± 65	90 ± 77	24 ± 26	58 ± 28	29 ± 11	52 ± 55	17 ± 7	0.000
AST, g/l	47 ± 40	65 ± 39	26 ± 19	74 ± 53	51 ± 16	48 ± 40	18 ± 3	0.000
VL, IU/ml	3.89E+06 (6.55E+05, 8.18E+06)	1.01E+06 (2.35E+05, 3.79E+06)	-	9.45E+05 (1.64E+05, 2.09E+06)	1.08E+07 (3.19E+06, 1.74E+07)	2.26E+06 (4.32E+06, 6.73E+06)	-	NA
WBC, $\times 10^9$/l	5.0 ± 1.0	4.4 ± 1.4	3.1 ± 1.1	3.0 ± 1.1	5.3 ± 1.3	3.9 ± 1.5	6.4 ± 1.1	0.000
PLT, $\times 10^9$/l	176 ± 55	154 ± 65	154 ± 57	62 ± 41	85 ± 57	140 ± 68	242 ± 41	0.000
Lymphocytes, $\times 10^9$/l	2.0 ± 0.5	1.9 ± 0.6	1.2 ± 0.5	1.1 ± 0.5	1.7 ± 0.6	1.5 ± 0.6	2.2 ± 0.4	0.000
Neutrophils, $\times 10^9$/l	2.4 ± 0.9	2.6 ± 1.1	1.6 ± 0.7	1.5 ± 0.6	2.7 ± 1.0	1.9 ± 0.9	3.7 ± 1.0	0.000
PLR	90 ± 28	88 ± 40	154 ± 85	61 ± 31	51 ± 23	105 ± 67	115 ± 23	0.326
NLR	1.33 ± 0.67	1.19 ± 0.69	1.52 ± 0.79	1.71 ± 1.43	1.92 ± 1.12	1.47 ± 0.92	1.79 ± 0.63	0.042

ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, female; HCV, hepatitis C virus; M, male; NA, not applicable; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelets; SD, standard deviation; VL, viral load; WBC, white blood cell count.
[a] Data are expressed as the mean ± SD, and for VL as the median (lower quartile, upper quartile).
[b] HCV-UT, HCV untreated group; HCV-UC, HCV uncleared group; HCV-Cl, HCV cleared group; HCV-Cirr, HCV-related cirrhosis group; HCV-HCC, HCV-related hepatocellular carcinoma group. HCV (groups) represent HCV-infected patients of different groups; HCV (total) represents all HCV-infected patients.
[c] *p*-Value for the comparison of HCV (total) and healthy control data.

17 ± 7, $p < 0.001$; AST 48 ± 40 vs. 18 ± 3, $p < 0.001$). In addition, HCV-infected patients in total (HCV (total)) had significantly lower WBC, PLT, lymphocyte, and neutrophil counts than healthy controls (WBC 3.9 ± 1.5 vs. 6.4 ± 1.1, $p < 0.001$; PLT 140 ± 68 vs. 242 ± 41, $p < 0.001$; lymphocytes 1.5 ± 0.6 vs. 2.2 ± 0.4, $p < 0.001$; neutrophils 1.9 ± 0.9 vs. 3.7 ± 1.0, $p < 0.001$). The characteristics of the patients in the different HCV-related disease groups are also shown in Table 1.

3.2. Comparison of PLR and NLR of patients with HCV infection at different disease stages

The association of PLR and NLR with the disease stage in HCV infection was investigated. As shown in Figure 1, it was found that the HCV-Cirr and HCV-HCC groups had lower PLR levels (61 ± 31 and 51 ± 23, respectively) in comparison with the HCV-Ht and healthy control groups (90 ± 28 and 115 ± 23, respectively); the differences were statistically significant ($p < 0.001$). For NLR, there was no changing trend in HCV infection. To summarize, PLR showed a decreasing trend along with HCV infection-related liver diseases.

3.3. Correlation of PLR and NLR with antiviral treatment outcomes in CHC patients

The correlation of PLR and NLR with hepatitis virus clearance in CHC patients was then evaluated. As shown in Figure 2, the PLR of the HCV-Cl group was significantly higher than that of the HCV-UT and HCV-UC groups (154 ± 85 vs. 90 ± 28, $p < 0.001$; 154 ± 85 vs. 88 ± 40, $p = 0.001$, respectively). However, the PLRs of the HCV-UT and HCV-UC groups showed no difference ($p = 0.589$). For NLR, no statistically significant change was found among the different groups HCV-UT, HCV-UC, and HCV-Cl.

ROC analysis for the prediction of virus clearance was conducted next. The ROC curve analysis for PLR showed an area under the curve (AUC) of 0.772 (95% confidence interval (CI) 0.674–0.869, $p < 0.000$), with a specificity of 92.3% and a sensitivity of 53.7%; for NLR, the AUC was 0.612 (95% CI 0.495–0.730, $p = 0.063$), with a specificity of 76.9% and a sensitivity of 48.8% (Figure 3). Taken together, PLR and NLR, especially PLR, showed good indicating function for HCV clearance: a stable lower PLR could imply an undesirable virological response.

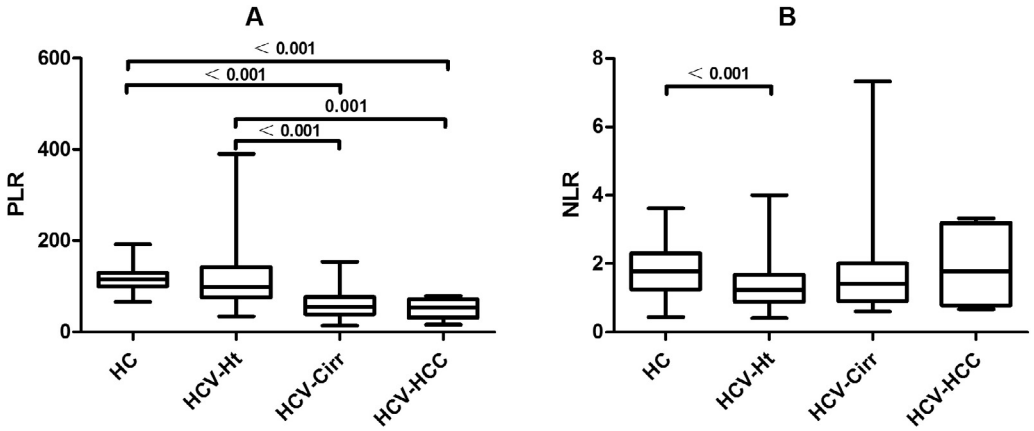

Figure 1. Comparison of PLR and NLR in HCV-Ht, HCV-Cirr, and HCV-HCC patients and healthy controls; the data are expressed as the mean ± SD (PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; HCV-Ht, HCV-related hepatitis group; HCV-Cirr, HCV-related cirrhosis group; HCV-HCC, HCV-related hepatocellular carcinoma group; HC, healthy controls).

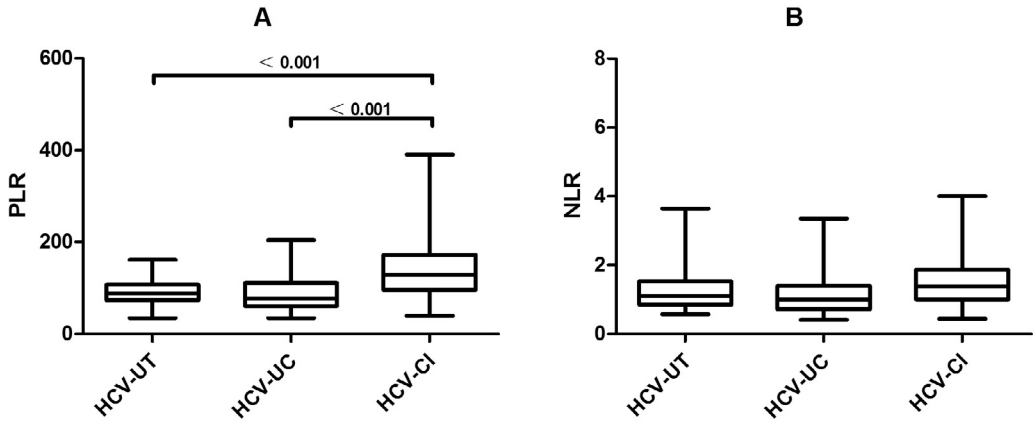

Figure 2. Comparison of PLR and NLR in CHC patients: HCV-UT, HCV-UC, and HCV-Cl patients, and healthy controls; the data are expressed as the mean ± SD (PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; CHC, chronic hepatitis C; HCV-UT, HCV untreated group; HCV-UC, HCV uncleared group; HCV-Cl, HCV cleared group).

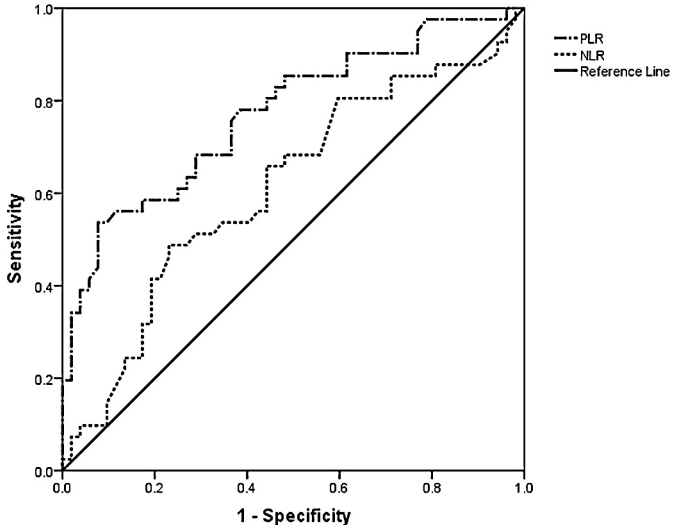

Figure 3. ROC curves grouped by PLR and NLR. The ROC for PLR is represented by the short dashed line (AUC = 77.2%, sensitivity 53.7%, specificity 92.3%) and the ROC for NLR is represented by the dotted line (AUC = 61.2%, sensitivity 48.8%, specificity 76.9%) (ROC, receiver operating characteristic; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; AUC, area under the curve).

3.4. Correlation of PLR and NLR with virological response in CHC patients treated with peg-interferon and ribavirin

Based on the above results, 24 regularly followed CHC patients were reviewed using clinical data obtained before treatment (week 0) and at weeks 4, 48, and 72 during treatment with peg-interferon and ribavirin. Six patients achieving both a rapid virological response and a sustained virological response (RVR&SVR), 12 patients achieving a sustained virological response only (SVR), and six patients not achieving a sustained virological response (non-SVR) were included. Comparing the PLRs of patients with the different virological responses, it was found that the PLR of the RVR&SVR group patients increased noticeably over time (Figure 4A). For patients in the SVR group, the PLR dropped slightly at week 4 and then increased gradually over time (Figure 4B). Conversely, for non-SVR patients, PLR did not rise and sometimes even dropped over time (Figure 4C). Of note, the NLR of patients with the different virological responses did not show the same tendency as the PLR over the treatment course (Figure 4D–F). Taken together, an increasing PLR in CHC patients was found to indicate a good virological response; a stable PLR or a downward trend in the PLR could predict no RVR achievement by week 4 and even no SVR by week 72.

4. Discussion

The PLR and NLR, known as systemic inflammatory biomarkers, are immune response-related indicators. Preoperative PLR and NLR have been considered to be related to the prognosis of aggressive tumors in various cancers. Many studies have confirmed that one or both of these is related to the progression and prognosis of cardiovascular diseases, sudden deafness, vestibular neuritis, and thrombosis-related diseases.[21–23] Meanwhile, the present authors have noted that chronic infectious diseases, including different types of viral hepatitis, are characterized by a persistent chronic inflammatory response, and the existing research has also confirmed that the PLR and NLR are associated with the progression and prognosis of viral hepatitis-related HCC.[13,14] As the carrier medium role of platelets for immune effector cells is being clarified,[9] the PLR, calculated as the PLT/lymphocyte count and showing the variation in both platelets and lymphocytes, and the NLR, calculated as the neutrophil count/lymphocyte count and showing the variation in both neutrophils and lymphocytes, comprehensively indicate an immune status change during the disease period. To date, no studies on the PLR and NLR in HCV infection-related diseases have been reported.

In the present study, by retrospective analysis of HCV-infected patients with different stages of liver disease and CHC patients with different virological responses to treatment with peg-interferon and ribavirin, it was found that the PLR is closely related to the stage of HCV infection-related liver disease and the virological response of CHC patients. Compared with healthy controls, the PLR of HCV-related cirrhosis and HCC patients were significantly reduced ($p < 0.001$), while that of CHC patients was not ($p = 0.061$). However, there was no significant difference between the PLR of HCV-related cirrhosis patients and that of HCV-related HCC patients ($p = 0.609$). Thus, a low PLR could predict an undesirable progression of HCV infection-related liver disease. Among the CHC patients, it was found that the PLRs of untreated patients and those who failed to reach the ideal virology clearance were reduced, and the PLR of patients with virus clearance was significantly increased. ROC curve analysis also confirmed that PLR was a good indicator of virus removal. Therefore, PLR is closely associated with HCV clearance. In contrast, the NLR for HCV-related liver disease stages and virus clearance in CHC patients did not show the same tendency, since there was not much significant change in the progression of HCV infection-related liver diseases.

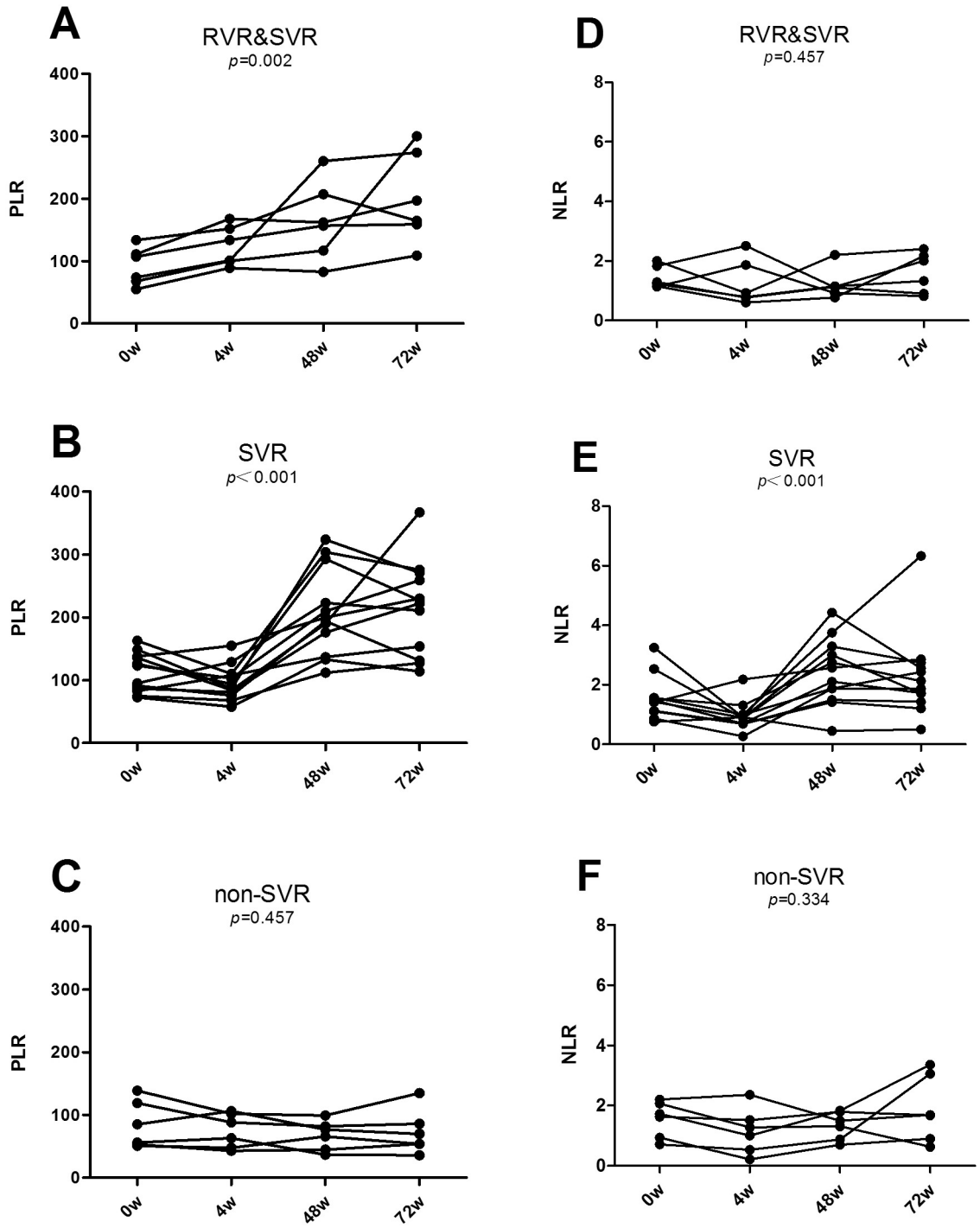

Figure 4. Correlation of PLR and NLR with different virological responses in CHC patients treated with peg-interferon and ribavirin: RVR&SVR, patients achieving both a rapid virological response and a sustained virological response; SVR, patients achieving a sustained virological response only; non-SVR, patients not achieving a sustained virological response. (A)–(C) PLRs of patients with different virological responses are shown. (D)–(F) NLRs of patients with different virological responses are shown. Every round black dot represents a single PLR or NLR value at the corresponding time. The *p*-values for the comparisons of the levels of PLR or NLR at different weeks during antiviral treatment were calculated with the Friedman test, a non-parametric repeated measures analysis of variance (ANOVA) (PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; CHC, chronic hepatitis C).

Taking into consideration that WBC, PLT, lymphocyte, and neutrophil counts are all vulnerable to infection and to a variety of other clinical diseases, and are inclined to great fluctuations,[24] patients were assigned to groups strictly according to the inclusion and exclusion criteria and, furthermore, the clinical data of 24 regularly followed CHC patients were reviewed. The PLRs of patients who failed to attain a SVR did not vary much, or were even slightly reduced over the course of treatment. The PLRs of patients who achieved SVR but not RVR showed a slightly reduced PLR during the early stage of antiviral treatment (week 4), and then an obvious increase in PLR to a higher level. The PLRs of patients achieving both RVR and SVR increased as soon as antiviral treatment was started and then increased gradually to a higher level. The apparent individual differences in the PLRs of patients

before treatment (week 0) should be noted; the virological response outcome was closely related to the variation tendency of the PLR but not to a single PLR value at a certain time point. Therefore, dynamic continuous monitoring of the patient's PLR would be of benefit for the surveillance of disease progression and prognosis.

The present study appears to be the first to show that PLR is related to the progression of HCV infection-related disease and the virological response outcome in CHC patients treated with peg-interferon and ribavirin. The correlation was confirmed by statistical analysis. However, there are a number of limitations to this study that should be emphasized. First, the study retrospectively analyzed a relatively small number of patients and controls. Accordingly, cause-and-effect relationships cannot be concluded; prospective longitudinal studies are required to elucidate any relationships. With a small sample size, caution must be taken, as the findings might not be transferable to other populations. Secondly, the evaluation of possible confounding factors, such as the occurrence of idiopathic thrombocytopenic purpura (ITP), diabetes mellitus, etc., was incomplete, and this needs to be taken into account. Future studies could evaluate whether PLR changes the same way as in HCV infection only. Moreover, this study was limited to those patients who attended the First Affiliated Hospital of Zhengzhou University. As a result, the findings might not be directly applicable to subjects from other ethnic groups. Ultimately, the patients being investigated were mainly infected with HCV genotype 1b, and the genotype of IL-28 was not taken into account. Further studies are needed to determine the latent correlations and mechanisms.

In summary, the current evidence showed that PLR, but not NLR, is closely related with HCV infection-related disease progression and the virological response outcome in CHC patients treated with peg-interferon and ribavirin. Regular follow-up monitoring of the PLR will contribute to disease surveillance, since an increasing tendency in PLR predicts a good virological response outcome. Further studies are needed to determine the exact mechanisms through which the patient's PLR changes with disease progression and antiviral treatment.

In conclusion, the PLR, better than the NLR, correlates tightly with HCV infection-related disease progression and the virological response outcome in CHC patients. Dynamic continuous monitoring of the PLR, rather than a single high or low PLR value at a certain time point, will contribute to disease surveillance, with an increasing tendency predicting a good virological response. Taken together, the platelet-to-lymphocyte ratio (PLR), superior to neutrophil-to-lymphocyte ratio (NLR), correlates with the disease severity of HCV infection.

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