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Potential utility of hemogram indices in hepatitis C virus-related vasculitis: a case–control study

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Abstract

Background Hemogram indices are simple, economic indicators of the systemic inflammation characteristic of autoimmune diseases including vasculitides. The clinical utility of hemogram indices in hepatitis C virus-related vasculitis (HCV-V) has not been established. This study aimed to evaluate neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), neutrophil/hemoglobin ratio (NHR), platelet/hemoglobin ratio (PHR), and systemic immune-inflammation index (SII) as potential biomarkers of HCV-V, and their relationship with disease activity. This cross-sectional case–control study was conducted in the departments of Rheumatology and Rehabilitation and Hepatogastroenterology, at Cairo University Hospital. Patients with HCV-V, patients with HCV infection free from extrahepatic manifestations (HCV sine vasculitis), and healthy control subjects were recruited. HCV-V activity was assessed using the Birmingham Vasculitis Activity Score (BVAS).

Results Twenty-four HCV-V patients, 21 HCV sine vasculitis patients, and 40 healthy controls were recruited. Age and sex distribution was similar across groups. In HCV-V patients, NLR, PLR, NHR, and SII were higher than healthy controls, with NLR (area under curve (AUC) 0.94, $p=0.002$), PLR (AUC 0.72, $p=0.007$), NHR (AUC 0.89, $p<0.001$) and SII (AUC 0.92, $p<0.001$) discriminating both groups. PHR correlated with BVAS ($r=0.53$, $p=0.007$) while NHR correlated with ESR ($r=0.55$, $p=0.007$). NLR, NHR, and SII were higher in HCV-V than HCV sine vasculitis patients, with NHR (AUC 0.74, $p=0.022$) and SII (AUC 0.75, $p=0.038$) discriminating in both groups.

Conclusion Hemogram indices are useful biomarkers of HCV-V. Longitudinal studies are recommended to explore the predictive power of HCV-infected patients developing vasculitis and their potential relationship with therapeutic response and disease relapse.

Keywords HCV, Vasculitis, Neutrophil to lymphocyte ratio, Platelet to lymphocyte ratio, Systemic immune inflammation index

Background

Besides being hepatotropic, the hepatitis C virus (HCV) is also lymphotropic [1]. HCV vasculitis (HCV-V) is one of the most prominent extra-hepatic manifestations of chronic HCV infection. Being a small to medium vessel vasculitis, palpable purpura, arthralgia, peripheral neuropathy (distal sensory or sensory-motor polyneuropathy) and membranoproliferative glomerulonephritis are its most common manifestations [2, 3]. While the use of direct-acting antiviral drugs would be expected to reduce the burden of HCV infection [4], HCV-V is still relevant,

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particularly in communities with limited access to therapy [1].

Indices calculated as ratios between hemogram components have been described as surrogates of systemic inflammation and the immune response [5, 6]. Examples include the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-hemoglobin ratio (NHR), platelet-to-hemoglobin ratio (PHR), and the systemic immune-inflammation index (SII). They have captured the interest of researchers because they are simple, objective, and cost-effective, and thus can be readily calculated by the clinician [6]. They have been studied as diagnostic and prognostic markers of several cancers [7, 8], chronic diseases [9, 10], and even psychiatric disorders [11]. Variations in hemogram indices in relation to healthy subjects were also reported in a multitude of autoimmune rheumatic disorders, often correlating with disease activity [6, 12, 13].

NLR and PLR have been previously studied as indicators of HCV-related parenchymatous liver disease [14], while both indices in addition to SII have been previously studied as biomarkers in various vasculitides [15–20], correlating with disease activity as well [15, 16, 20, 21]. While NHR and PHR have not previously been studied in vasculitides, PHR is an established prognostic biomarker of cardiovascular disease [10, 22] and both have been previously studied in rheumatoid arthritis [12].

The role of hemogram indices as biomarkers of the presence of HCV-V has not been defined. Thus, the aim of this study was to explore the potential utility of hemogram indices in HCV-V and to examine their potential relationship with disease activity.

Patients and methods

This case–control cross-sectional study recruited participants from the Hepatogastroenterology and Rheumatology and Rehabilitation Departments at Cairo University Hospitals, between January 2022 and December 2023. The protocol of this study was approved by the Cairo University Faculty of Medicine Research Ethical Committee (MS-441–2021) and conformed to the principles laid down by the Declaration of Helsinki and its amendments. All participants provided informed consent prior to their inclusion.

Subject recruitment

Participants were recruited into one of three groups:

HCV-V group: patients with recently discovered (within 3 months) untreated HCV infection, presenting additionally with one or more extrahepatic manifestations of HCV infection, judged to have currently active HCV-V, according to rheumatologist opinion. HCV infection was defined as a positive anti-HCV-antibody test and/or detectable viremia by HCV ribonucleic acid polymerase chain reaction (HCV-RNA PCR). Extrahepatic manifestations of HCV infection included: fever ≥ 37.5 with no identifiable cause, arthritis/arthralgia, palpable purpura, skin ulcers, digital ischemia/gangrene, Raynaud's phenomenon, peripheral neuropathy, cranial nerve involvement, vasculitic central nervous system involvement, intestinal vasculitis, membranoproliferative glomerulonephritis or pulmonary involvement. Disease activity was assessed using the Birmingham Vasculitis Activity Score (version 3) [23].

HCV sine vasculitis group: patients with recently discovered untreated HCV infection, as defined above, whose comprehensive medical history and clinical examination confirmed them to be free from any extrahepatic manifestations of HCV infection. Patients with significant liver cell failure (Child–Pugh classes B or C) and/or hepatocellular carcinoma on initial evaluation were excluded.

Control group: apparently healthy HCV-negative subjects (as ascertained by negative HCV antibodies and no detectable viremia by HCV-RNA PCR).

Exclusion criteria

For all recruited subjects, subjects with age < 18 years, pregnancy or lactation, active malignancy, recent significant bleeding and/or blood or blood product transfusion (within 8 weeks), the concomitant diagnosis of any primary autoimmune disease, and other chronic viral infections (hepatitis B virus and/or human immunodeficiency virus) were excluded.

For the HCV-V group, patients whose clinical and/or serological presentation was compatible with other primary or secondary vasculitides (e.g., anti-neutrophil cytoplasmic antibodies associated with vasculitis) were excluded.

Laboratory assessment

All subjects underwent blood sampling to obtain a hemogram (complete blood count) within 24-h of their clinical evaluation. For HCV-V patients, erythrocyte sedimentation rate (ESR), serum complement component levels (C3 and C4), RF, and cryoglobulins were additionally assayed. Blood sampling from HCV-infected patients was undertaken before the commencement of antiviral and/or immunosuppressive therapies.

Hemogram indices

Blood cell ratios were calculated as follows: NLR and PLR were calculated using absolute neutrophil, lymphocyte,

and platelet counts. NHR and PHR were calculated by dividing the absolute neutrophil and platelet counts by the hemoglobin concentration, respectively. The systemic immune-inflammation index (SII) was calculated by multiplying the NLR by the platelet count [15].

Statistical analysis

Data was reported as mean ± standard deviation (SD) for continuous variables, and frequencies (numbers and percentages) for categorical variables. Comparison of numerical variables between the study groups was done using *T* test or analysis of variance test with Games-Howell post hoc tests whenever appropriate. For comparing categorical data, Chi-square (χ^2) or Fisher's exact test was used whenever appropriate. Spearman rank correlation coefficients (r) were calculated to examine relationships between continuous variables. Linear regression analyses were utilized to examine possible predictors of the BVAS in HCV-V patients. Univariate logistic regression analyses with receiver operator characteristics (ROC) curves were utilized to determine optimal cutoff values of hemogram indices discriminating HCV-V patients from HCV sine vasculitis patients and healthy controls. Two-sided *p* values < 0.05 were considered statistically significant. Statistical calculations were performed on Jamovi 2.3 [24] on Microsoft Windows.

Results

A total of 24 (M:F = 11:13) subjects were recruited into the HCV-V group, 21 (M:F = 12:9) into the HCV sine vasculitis group, and 40 (M:F = 18:22) into the control group. No significant differences regarding sex distribution were observed between the 3 groups ($p = 0.641$). The mean age of HCV-V patients was 51.8 ± 11.6 years, of HCV sine vasculitis patients was 47.0 ± 12.0 years, and of control subjects was 47.5 ± 12.2 years ($p = 0.289$). A summary of the clinical presentations observed among HCV-V patients is displayed in Table 1.

Regarding treatment of HCV-V patients, 20(83.3%) required pulse steroid therapy (methylprednisolone) to control their disease activity, while the remaining 4(16.7%) were managed with oral steroids. Regarding immunosuppressive therapy, 15(83.3%) received cyclophosphamide, of whom one required concomitant rituximab and plasmapheresis, while 7(29%) received azathioprine, and 2(11.1%) were prescribed leflunomide.

Regarding serologic parameters, among HCV-V patients, C3 was consumed in four patients 4 (19%) while C4 was consumed in 7(33.3%). Rheumatoid factor was positive in 8 (38%) patients and cryoglobulins were detectable in 10 (47.6%). Ten patients (47.6%) fulfilled the classification criteria of cryoglobulinemic vasculitis [25]. A comparison of laboratory parameters and hemogram indices between the three recruited groups is outlined in Table 2.

Table 1 Clinical characteristics of recruited patients with HCV vasculitis

Clinical feature (n = 24)	*Frequency*
Arthralgia/arthritis	12(50)
Palpable purpura	12(50)
Sensory peripheral neuropathy	11(45.8)
Digital gangrene	9(37.5)
Mononeuritis multiplex	6(25.0)
Membranoproliferative glomerulonephritis	5(20.8)
Fever	5(20.8)
Cutaneous ulcers	4(16.7)
Weight loss	3(12.5)
Interstitial lung disease	2(8.3)
Raynaud's phenomenon	2(8.3)
Vasculitic CNS involvement	4(4.3)

Values are expressed as numbers (%). *CNS* central nervous system, *HCV* hepatitis C virus

The mean BVAS for HCV-V patients was 10.7 ± 5.8 points. BVAS showed significant correlation with the platelet count ($r = 0.45$, $p = 0.029$), and PHR ($r = 0.53$, $p = 0.007$), but not with hemoglobin concentration ($r = -0.39$, $p = 0.060$), total leukocyte count ($r = 0.21$, $p = 0.323$), NLR ($r = 0.13$, $p = 0.546$), PLR ($r = 0.33$, $p = 0.119$), SII ($r = 0.26$, $p = 0.207$), HCV-RNA PCR load ($r = 0.25$, $p = 0.376$) or ESR ($r = 0.34$, $p = 0.113$). Only the platelet count ($\beta = 0.02$, $p = 0.025$) and PHR ($\beta = 0.20$, $p = 0.007$) were significant predictors of the BVAS.

Among patients with HCV-V, ESR correlated with NHR ($r = 0.55$, $p = 0.007$), but not with PHR ($r = -0.19$, $p = 0.387$), NLR ($r = 0.25$, $p = 0.256$), PLR ($r = 0.29$, $p = 0.185$) or SII ($r = 0.24$, $p = 0.281$). NLR and PLR correlated with each other among HCV-V patients ($r = 0.60$, $p = 0.002$) and healthy controls ($r = 0.71$, $p < 0.001$) but not in HCV sine vasculitis patients ($r = 0.18$, $p = 0.425$).

ROC curves were plotted to determine optimal cutoff values of various hemogram indices to discriminate HCV-V patients from HCV sine vasculitis patients and control subjects (Table 3).

Discussion

The most characteristic extrahepatic manifestation of chronic HCV infection is HCV-V, a small to medium vessel vasculitic syndrome with significant morbidity and mortality [2, 4]. Hemogram indices have been investigated as simple economic biomarkers and prognostic indicators of a range of malignancies, chronic diseases, and autoimmune rheumatic disorders, including several vasculitides [6, 9, 10, 12, 15, 26]. Yet, the role of

Table 2 Laboratory parameters in recruited groups

Parameter	HCV-V	HCV sine vasculitis	Control	*P* value		
				HCV-V vs. HCV sine vasculitis	HCV-V vs. control	HCV sine vasculitis vs. control
Viral load (million/mL)	4.12 ± 1.1	0.91 ± 1.26	N/A	0.279	N/A	
Hemoglobin concentration (g/dL)	11.5 ± 2.1	12.9 ± 1.3	12.3 ± 2.1	**0.016**	0.332	0.240
Total leukocyte count (10^3/mm^3)	9.5 ± 3.9	6.8 ± 2.3	7.2 ± 1.6	**0.018**	**0.027**	0.754
Neutrophil count (10^3/mm^3)	6.3 ± 3.5	3.8 ± 1.8	2.2 ± 0.5	**0.011**	**< 0.001**	**0.001**
Lymphocyte count (10^3/mm^3)	2.5 ± 1.5	2.4 ± 0.6	4.3 ± 1.3	0.977	**< 0.001**	**< 0.001**
Platelet count (10^3/mm^3)	264.4 ± 124.9	198.1 ± 56.9	290.4 ± 60.3	0.065	0.611	**< 0.001**
Neutrophil/lymphocyte ratio	3.8 ± 3.7	1.6 ± 0.6	0.5 ± 0.2	**0.018**	**< 0.001**	**< 0.001**
Platelet/lymphocyte ratio	154.6 ± 130.8	92.1 ± 60.6	73.7 ± 27.3	0.106	**0.017**	0.396
Neutrophil/hemoglobin ratio	5.7 ± 2.4	4.2 ± 0.7	2.6 ± 0.6	**0.024**	**< 0.001**	**< 0.001**
Platelet/hemoglobin ratio	23.6 ± 15.3	15.5 ± 5.2	24.7 ± 8.1	0.057	0.939	**< 0.001**
Systemic Immune Inflammation Index	956.3 ± 860.1	323.6 ± 172.9	158.9 ± 66.6	**0.005**	**< 0.001**	**< 0.001**

Values are expressed as means ± standard deviations. Bold values are statistically significant ($p < 0.05$); *HCV-V* hepatitis C virus-associated vasculitis, *N/A* not applicable

Table 3 Cutoff values of various hemogram indices differentiating the three groups of recruited subjects

Parameter	*p* value	Cut off	AUC	95% CI	Sensitivity	Specificity	Accuracy
HCV-V vs. HCV sine vasculitis							
NLR	0.05	–	–	–	–	–	–
PLR	0.082	–	–	–	–	–	–
NHR	**0.022**	6.2	0.74	0.59–0.89	54.1	100	0.75
SII	**0.038**	664.6	0.75	0.61–0.89	45.8	100	0.71
HCV-V vs. control							
NLR	**0.002**	0.9	0.94	0.87–1.00	91.7	97.5	0.95
PLR	**0.007**	152.4	0.72	0.59–0.85	37.5	100	0.76
NHR	**< 0.001**	4.0	0.89	0.79–0.98	83.3	97.5	0.92
SII	**< 0.001**	224.0	0.92	0.84–0.99	91.7	85.0	0.88
HCV sine vasculitis vs control							
NLR	**0.007**	0.90	0.98	0.94–1.00	95.2	100	0.98
PLR	0.151	–	–	–	–	–	–
NHR	**< 0.001**	3.4	0.96	0.89–1.00	90.5	95.0	0.93
SII	**< 0.001**	248.2	0.82	0.69–0.94	61.9	90.0	0.80

Bold values are statistically significant ($p < 0.05$). *AUC* area under the curve, *CI* confidence interval, *HCV-V* hepatitis C virus-associated vasculitis, *NHR* neutrophil/hemoglobin ratio, *NLR* neutrophil/lymphocyte ratio, *PHR* platelet/hemoglobin ratio, *PLR* platelet/lymphocyte ratio, *SII* systemic immune inflammation index

hemogram indices as biomarkers of HCV-V has not been established. Thus, the aim of this study was to examine the relationship between five hemogram indices (namely NLR, PLR, NHR, PHR, and SII) and the presence of vasculitis in HCV-infected patients as well as to examine their potential relationship with disease activity.

In this study, articular involvement and palpable purpura were each encountered in half the cases, being the most frequent manifestations of HCV-V in this cohort. This finding agrees with a previous report from Egypt [27]. Neurological involvement was evident in 75%, renal involvement in 20.8%, and pulmonary involvement in 8.3% of patients recruited in this study. These frequencies are also within range of those observed in an Egyptian multicenter study by Shahin et al., who documented musculoskeletal involvement in 50.3%, purpura in 62.3%, neurologic involvement in 61.6%, nephritis in 17.2% and pulmonary involvement in 7.3% of HCV related vasculitis patients [4]. The frequencies of purpura (65–86%), articular affection (31–92%), glomerulonephritis (15–33%), and peripheral neuropathy (50–79%) have been reported in several European

cohorts of HCV-related vasculitis [28–30] and are concordant with our findings.

Examining blood cell counts, HCV-V patients recruited in this study had higher total leukocyte and absolute neutrophil counts, as well as lower absolute lymphocyte counts compared to controls. A decrease in lymphocytes and an increase in neutrophils in comparison to healthy subjects was also noted in a previous study on granulomatosis with polyangiitis (GPA) [18]. These observations are likely related to the excessive inflammatory process seen in small to medium-sized vasculitic disorders [5]. On the other hand, HCV sine vasculitis patients in this study had significantly lower platelet counts compared to controls, which is consistent with the previously reported hematologic effects of HCV infection [14].

In this work, HCV-V patients exhibited higher NLR, PLR, NHR, and SII compared to controls. Elevations in NLR and PLR compared to healthy subjects are consistent with findings in cohorts of patients with Takayasu's arteritis [16], Behçet's disease [20], and GPA [18, 31], while elevations in PLR but not NLR were documented in patients with giant cell arteritis [17]. In contrast, El-Husseiny et al. reported no significant difference in NLR and PLR from healthy subjects in 30 Egyptian patients with different primary vasculitides [26]. The mixed nature of their cohort may explain this discordance with our findings.

In the present work, NLR, NHR, and SII were significantly higher in patients with HCV-V compared to HCV sine vasculitis patients. Regarding the capacity to discriminate between both groups, NLR failed, while NHR and SII were highly specific at the cost of poor sensitivity. Thus, apart from their status as diagnostic biomarkers of RA and adult-onset Still's disease respectively [12, 13], NHR and SII seem to be promising as useful biomarkers of HCV-V.

In the present study, BVAS and ESR exhibited no significant relationship with each other among HCV-V patients. This could be explained by the observation that traditional inflammatory markers (e.g., ESR or C-reactive protein), though commonly used to monitor disease activity in vasculitides, do not always correlate with inflammatory activity in the vascular wall [17]. Since different hemogram indices act as surrogates of systemic inflammation and the immune response [6, 16], a significant relationship with BVAS in HCV-V patients was anticipated. In this work, PHR and the platelet count positively correlated with and predicted the BVAS in HCV-V patients, while NHR correlated with the ESR. Although neither has been previously studied in vasculitides, PHR, but not NHR, has been previously demonstrated to correlate with disease activity in RA [12]. As for the SII, it failed to correlate with BVAS or ESR in HCV-V patients of this study. While it was described as a predictor of higher disease activity in GPA, predicting poorer outcomes [15], its role as an indicator of HCV-V activity seems to be limited.

Additionally, neither NLR nor PLR correlated with BVAS or ESR among the studied HCV-V patients. Previous studies examining the relationship between NLR and PLR with disease activity and traditional inflammatory markers in different vasculitides yielded mixed results. In Takayasu arteritis, higher NLR and PLR predicted disease activity and correlated with ESR [16]. In Behçet's disease, PLR but not NLR correlated with disease activity [20, 26]. Neither NLR nor PLR correlated with BVAS or ESR in a mixed cohort of primary vasculitides patients [26]. In GPA, a correlation of NLR with BVAS and ESR was documented in one study [21] but not another [18] while PLR correlated with ESR but not BVAS [31]. Further large-scale studies are needed to establish the role of hemogram indices as surrogates of disease activity in different forms of vasculitis.

Chronic infectious diseases, including different types of viral hepatitis, are characterized by a chronic low-grade systemic inflammatory response [14, 32] Thus, it is not surprising that NLR, NHR, and SII were significantly higher in patients with HCV sine vasculitis in this study than in control subjects, successfully discriminating both groups. Interestingly, PLR was not significantly different between both groups, which is contrary to previously reported data on patients with HCV infection. In a cohort of Chinese patients with HCV infection, PLR and NLR in untreated patients were significantly lower than in healthy subjects [14]. These patients were also relatively younger than the HCV sine vasculitis patients in this study, therefore age and ethnicity variations in hemograms may explain these discrepant results [5].

While this study is novel in exploring the relationship between hemogram indices and HCV-V, it is not without shortcomings, namely its cross-sectional design, single-centered and limited number of patients. Limitations of studies on hemogram indices in general are also applicable here [5]. While the confounding effect of treatment on hemogram indices was avoided in this study, the effect of seasonal variation on blood cell counts was not. The use of cut-off values to predict HCV-V is also limited by the need to correct demographic confounders, including sex, age, and ethnicity. On the research agenda, longitudinal studies are needed to determine whether hemogram indices would predict the development of vasculitis in HCV-infected patients, change in response to treatment, or forecast disease relapse. Moreover, whether hemogram indices would act as a cost-effective means to differentiate HCV-V from other small to medium-vessel vasculitides, remains to be explored.

Conclusion

Compared to healthy subjects, four hemogram indices (NLR, PLR, NHR, and SII) were biomarkers of the presence of HCV-V, with PHR correlating with disease activity. NHR and SII also could potentially discriminate patients with HCV sine vasculitis from both HCV-V patients and healthy subjects. Hemogram indices are simple and economic, thus longitudinal studies on HCV-infected patients are recommended to explore their predictive power of the development of vasculitis and their dynamics in relation to therapeutic response and disease relapse, if any.

Abbreviations

AUC	Area under the curve
BVAS	Birmingham vasculitis activity score
CI	Confidence interval
ESR	Erythrocyte sedimentation rate
F	Female
GPA	Granulomatosis with Polyangiitis
HCV	Hepatitis C virus
HCV-V	HCV-related Vasculitis
M	Male
NHR	Neutrophil hemoglobin ratio
NLR	Neutrophil lymphocyte ratio
PCR	Polymerase chain reaction
PHR	Platelet/hemoglobin ratio
PLR	Platelet lymphocyte ration
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RNA	Ribonucleic acid
ROC	Receiver operator characteristics
SD	Standard deviation
SII	Systemic immune inflammation index

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Authors' contributions

SF and DA conceptualized the research project. AH, BE, and MA oversaw participant recruitment and data collection. BE and AH performed data handling and analysis. DA wrote the first draft of the manuscript. DA and SF revised the draft for publication. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Cairo University Faculty of Medicine Research Ethical Committee (MS-441–2021) and has thus been conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All participants have provided informed consent prior to their inclusion.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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