Effect of direct-acting antivirals on platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in patients with hepatitis C virus-related thrombocytopenia
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Objectives
To study the effect of direct-acting antivirals (DAAs) on platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) in patients with hepatitis C virus (HCV)-related thrombocytopenia.

Background
PLR and NLR are correlated with HCV infection, HCV-related liver cirrhosis, HCV-related atherosclerosis and cardiovascular diseases.

Patients and methods
In the current study, we studied 100 patients with HCV-related thrombocytopenia. All patients were subjected to anti-HCV antibody, HBsAg, liver profile, blood urea, serum creatinine, fasting and postprandial blood glucose, complete blood count, iron profile, direct anti-globulin test, rheumatoid factor, antinuclear antibody, and alpha fetoprotein. Abdominal ultrasound, FibroScan, echocardiography, and electrocardiography were done for all patients. Thrombocytopenia was defined as platelets count less than 150,000/mm. The used DAAs were sofosbuvir and daclatasvir, and duration of treatment was 12 weeks. All patients were followed up during antiviral therapy (for 12 weeks) and had extended follow-up for 24 weeks after the end of therapy with DDAs. Quantitative PCR for HCV RNA was done at the start of therapy and at 12 weeks (end of treatment response). PCR for HCV was repeated at 12 weeks after the end of treatment to assess the sustained viral response at 12 weeks after end of treatment (SVR-12) and at 24 weeks after the end of treatment to assess the sustained viral response at 24 weeks after end of treatment (SVR-24). PLR and NLR were calculated by dividing platelet and neutrophil counts, respectively, by lymphocyte count at the start of treatment, then at 4 weeks, at 12 weeks (end of treatment), at 24 weeks (SVR-12), and at 36 weeks (SVR-24).

Results
The mean age of patients was 49.55±7.79 years, with a range of 33–64 years. They showed female predominance, with females constituting 58.7%. Patients were all Child A status. Liver fibrosis stage was either stages I, II, or III (45, 30, and 25%, respectively). Mean platelet count was 82.25±23.64, 77.01±18.58, 90.84±18.86, 85.02±18.79, and 90.26±18.67 before starting treatment with DAAs, at 4 weeks, at 12 weeks (end or treatment), at 24 weeks (SVR-12), and at 36 weeks (SVR-24), respectively. PLR mean±SD was 74.07±12.76, 76.01±13.58, 65.84±13.86, 62.02±12.79, and 60.26±12.67 before starting treatment with DAAs, at 4 weeks, at 12 weeks (end or treatment), 24 weeks (SVR-12), and at 36 weeks (SVR-24), respectively. NLR mean±SD was 1.61±0.24, 1.64±0.23, 1.50±0.24, 1.45±0.23, and 1.33±0.24 before starting treatment with DAAs, at 4 weeks, 12 weeks (end or treatment), 24 weeks (SVR-12), and at 36 weeks (SVR-24), respectively. Both PLR and NLR initially increased at 4 weeks after the start of treatment and then both significantly decreased to reach lowest level at 36 weeks (SVR-24).

Conclusion
PLR and NLR are both decreased after HCV eradication by DDAs in HCV-infected patients with thrombocytopenia suggesting improvement of HCV-associated systemic inflammation.

Keywords:
direct-acting antivirals, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

Introduction
The global prevalence of hepatitis C virus (HCV) infection was estimated at 1% in 2015 and therefore approximately 71 million people worldwide are still...
considered to be infected [1]. The burden of HCV infection in Egypt is very high. Approximately 15% of the adult population are seropositive for HCV, and more than four million individuals remain viremic [2]. Most HCV cases are subclinical, leading to eventual chronic liver injury that can lead to chronic inflammation of the liver and progressive fibrosis. Furthermore, 25% of patients can develop liver cirrhosis and hepatocellular carcinoma [3]. Beside local hepatic inflammation, a concomitant low-grade systemic inflammation has been suggested in several studies, as suggested by high proinflammatory cytokine levels and blood monocytes activation in individuals with chronic HCV infection. Moreover, chronic HCV infection has been associated with oxidative stress activation, which may play a role in the development of local and systemic inflammation [4]. Chronic HCV infection was associated with an increased risk of subclinical atherosclerosis, myocardial injury, peripheral artery disease, and cerebrovascular and cardiovascular events [5,6]. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are novel inflammatory biomarkers used as prognostic factors in various diseases. They can be easily calculated and are widely available but they may be affected by several inflammatory conditions [7,8]. NLR has recently emerged as a new important inflammatory marker for predicting cardiovascular events [9], insulin resistance (IR) [10], and atherosclerotic plaques [11]. The PLR has been considered as inflammatory marker that can predict thrombotic events [12] and severe atherosclerosis [13]. Current hepatitis C treatments are made up of combinations of drugs called direct-acting antivirals (DAAs). DAAs target specific nonstructural proteins of the virus and result in disruption of viral replication and infection. The four classes of DAAs, which are defined by their mechanism of action and therapeutic target, are NS5B nucleoside polymerase inhibitors, nonstructural proteins 3/4A (NS3/4A) protease inhibitors, NS5B non-nucleoside polymerase inhibitors, and NS5A inhibitors [14]. It is confirmed that cellular immunity has an important role in the development of HCV infection, whereas different cell factors are also involved [15–17]. Different subgroups of lymphocytes, like the effector T-cells, regulatory T-cells, and cytotoxic T-cells, also play an important role in HCV infection [18]. There are preliminary evidences that HCV clearance by DAA induces a restoration of cytokines and inflammatory markers involved in the development of atherosclerosis [19,20], although the data seem to indicate that this improvement was less sustained in HCV-infected patients with advanced liver disease [21]. The aim of this work was to study the effect of DAAs on PLR and NLR in patients with HCV-related thrombocytopenia.

### Patients and methods

One hundred patients with HCV-related thrombocytopenia were selected from out-patient and in-patient clinics of Hepatology and Hematology Units, Menoufia University Hospital, in the period from June 2016 to June 2018. Informed consents were obtained from all patients in accordance with the local ethical committee. All patients were subjected to medical history taking and complete physical examination. Investigations were done for all patients, including anti-HCV antibody, HBsAg, liver profile (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, serum albumin, total bilirubin, direct bilirubin, prothrombin time and concentration, and international normalized ratio), blood urea, serum creatinine, fasting and postprandial blood glucose, complete blood count, blood film, iron profile, direct anti-globulin test, rheumatoid factor, antinuclear antibody, alpha fetoprotein, thyroid-stimulating hormone, and serum *Helicobacter pylori* antibodies detection. Abdominal ultrasound was performed. ECG and echocardiography were done to detect coronary heart disease. HCV RNA by PCR nested quantitative by IU/ml was done for all patients. Transient elastography measurement using FibroScan was performed for all patients to assess the stage of liver fibrosis. Patients with stage 4 fibrosis were excluded. Thrombocytopenia was defined as platelets count less than 150,000/mm. Patients included in this study are adults (≥18 years old) with compensated chronic HCV infection (child A) associated with thrombocytopenia (platelets >150,000/mm). Patients aged less than 18 years old and patients with splenomegaly, systemic lupus erythematosus, rheumatoid arthritis, thyroid disorders, chronic kidney disease, iron-deficiency anemia, peripheral vascular disease, coronary heart disease, prior interferon therapy, decompensated liver disease, concomitant hepatitis B infection, HIV infection, hepatocellular carcinoma, *H. pylori* infection, diabetes mellitus, and hematological and nonhematological malignancies were excluded from this study. Patients who started treatment for thrombocytopenia either by corticosteroids or platelet growth factors were also excluded. Bone marrow examination was done for patients aged more than 60 years to exclude other causes of thrombocytopenia, especially myelodysplastic syndromes. The used DAAs were sofosbuvir and daclatasvir for 12-week duration. All patients were followed up during antiviral therapy (for 12 weeks) and had extended follow-up for 24 weeks after the end of therapy with DAAs. Complete blood count was done at the start of treatment with DAAs, at 4 weeks, at 12 weeks (end of treatment), at 24 weeks (12 weeks...
after the end of treatment with DDAs), and at 36 weeks (24 weeks after the end of treatment with DDAs) to follow-up the degree of thrombocytopenia and calculate PLR and NLR at different stations of treatment with DDAs and at 12 and 24 weeks after the end of treatment. PCR for HCV RNA (using sensitive molecular method with a lower limit of detection ≤15 IU/ml) was done at the start of therapy and at 12 weeks (end of treatment response). PCR for HCV is repeated at 12 weeks after the end of treatment to assess the sustained viral response at 12 weeks after end of treatment (SVR-12) and at 24 weeks after the end of treatment to assess the sustained viral response at 24 weeks after end of treatment (SVR-24). All patients included in this study were HCV viral response at 24 weeks after end of treatment (SVR-24). Patients were all Child A status. Liver fibrosis stage was either stages I, II, or III (45, 30, and 25%, respectively). Baseline laboratory investigations of the studied patients are detailed in Table 1. Platelets number, NLR, and PLR of the studied group are detailed in Table 1. Platelets number, NLR, and PLR of the studied group

### Table 1 General characteristics and laboratory investigations of the studied group

| General characteristics | Patients (N=100) |
|-------------------------|-----------------|
| Age (years)             | 49.55±7.79      |
| Range                   | 33–64           |
| Sex                      |                |
| Female                  | 59 (59)         |
| Male                    | 41 (41)         |
| Fibrosis stage           |                |
| I                       | 45 (45)         |
| II                      | 30 (30)         |
| III                     | 25 (25)         |
| Baseline investigations  |                |
| Albumin (mean±SD) (g/dl)| 3.98±0.54       |
| Bilirubin (mg/dl)       | 0.9±0.22        |
| INR                     | 1.1±0.17        |
| ALT (U/ml)              | 30.0±22.0       |
| AST (U/ml)              | 36.65±27.60     |
| Hb (g/dl)               | 13.62±1.63      |
| Platelets (×10⁹/l)      | 82.78±25.38     |
| WBCs (×10⁹/l)           | 4.87±1.38       |
| Lymphocytes (×10⁹/l)    | 1.11±0.6        |
| Neutrophils (×10⁹/l)    | 1.79±1.2        |
| AFP (ng/ml)             | 2.94±3.53       |

AFP, alpha fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; INR, international normalized ratio; WBC, white blood cell.

**Statistical analysis**

Results were statistically analyzed by SPSS, version 20 (SPSS Inc., Chicago, Illinois, USA). Friedman test is a single test used to collectively indicate the presence of any significant difference between several time sequences for a not normally distributed quantitative variable, and then post-hoc test was used to show any significant difference between the individual groups or different time sequences. Significant difference was stated if P value was less than 0.05.

**Results**

General characteristics of the studied group are detailed in Table 1. The mean age of patients was 49.55±7.79 years, with a range of 33–64 years. They showed female predominance with females constituting 58.7%. Patients were all Child A status. Liver fibrosis stage was either stages I, II, or III (45, 30, and 25%, respectively). Baseline laboratory investigations of the studied patients are detailed in Table 1. Platelets number, NLR, and PLR of the studied group are detailed in Table 2. Platelet mean ±SD was 82.25±23.64, 77.01±18.58, 90.84±18.86, 85.02±18.79, and 80.26±18.67 before starting treatment with DDAs, at 4 weeks, at 12 weeks (end of treatment), at 24 weeks (SVR-12), and at 36 weeks (SVR-24), respectively. The platelet counts significantly decrease at 4 weeks, then reach its peak of increase at 12 weeks, then decrease at 24 weeks (SVR-12) and reached its lowest level at 36 weeks (SVR-24) (Fig. 1). PLR mean±SD was 74.07±12.76, 76.01±13.58, 65.84±13.86, 62.02±12.79, and 60.26±12.67 before starting treatment with DDAs, at 4 weeks, at 12 weeks (end or treatment), at 24 weeks (SVR-12), and at 36 weeks (SVR-24), respectively. PLR significantly showed initial increase at 4 weeks and then significantly decrease at 12 weeks (end of treatment) and at 24 weeks (SVR-12) and reach lower level at 36 weeks (SVR-24) (Fig. 1). NLR mean±SD was 1.61±0.24, 1.64±0.23, 1.50±0.24, 1.45±0.23, and 1.33±0.24 before starting treatment with DDAs, at 4 weeks, at 12 weeks (end or treatment), at 24 weeks (SVR-12), and at 36 weeks (SVR-24), respectively. NLR significantly showed initial increase at 4 weeks and then significantly decrease at 12 weeks (end of treatment) and at 24 weeks (SVR-12) and reach lower level at 36 weeks (SVR-24) (Fig. 1).

**Discussion**

The PLR and NLR are considered immune response-related indicators so they are known as systemic inflammatory biomarkers. It has been confirmed that PLR and NLR are related to the progression and prognosis of cardiovascular disorders and thrombotic events [7,8,11,22,23]. Chronic HCV infection causes hepatic and systemic inflammation, and it has been hypothesized that direct and indirect mechanisms can
be involved in the development of atherosclerosis via increased levels of pro-atherogenic chemokines and cytokines and inducing pro-atherogenic metabolic factors [4]. HCV also interferes with glucose and lipid metabolism, leading to IR and diabetes, which are known factors that induce atherosclerosis [5]. Chronic inflammation, endothelial dysfunction, and direct invasion of the arterial wall have also been cited as possible mechanisms [24]. As the carrier medium role of platelets for immune effector cells is being clarified [25], the PLR shows the variation in both platelets and lymphocytes, and the NLR shows the variation in both neutrophils and lymphocytes, comprehensively indicating an immune status change during the disease period [26]. It is seemed that the elimination of HCV by DAAs improves atherosclerosis.

### Table 2 Platelets, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio of the studied patients

| Patients (N=100) | Platelets | PLR | NLR |
|------------------|-----------|-----|-----|
| Mean±SD | Friedman test | P value | Post-hoc test |
| Platelets | | | |
| Baseline [1] | 82.25±23.64 | 236.15 | <0.001 | All P<0.001 except P4>0.05 |
| At 4 weeks [2] | 77.01±18.58 | | |
| At 12 weeks [4] | 90.84±18.86 | | |
| At 24 weeks [5] | 85.02±18.79 | | |
| At 36 weeks [6] | 80.26±18.67 | | |
| PLR | | | |
| Baseline [1] | 74.07±12.76 | 387.55 | <0.001 | P1–P16<0.001 |
| At 4 weeks [2] | 76.01±13.58 | | |
| At 12 weeks [4] | 65.84±13.86 | | |
| At 24 weeks [5] | 62.02±12.79 | | |
| At 36 weeks [6] | 60.26±12.67 | | |
| NLR | | | |
| Baseline [1] | 1.61±0.24 | 400.0 | <0.001 | P1–P16<0.001 |
| At 4 weeks [2] | 1.64±0.23 | | |
| At 12 weeks [4] | 1.50±0.24 | | |
| At 24 weeks [5] | 1.45±0.23 | | |
| At 36 weeks | 1.33±0.24 | | |

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. P1, 1 versus 2; P2, 1 versus 3; P3, 1 versus 4; P4, 1 versus 5; P5, 1 versus 6; P7, 2 versus 3; P8, 2 versus 4; P9, 2 versus 5; P10, 2 versus 6; P11, 3 versus 4; P12, 3 versus 5; P13, 3 versus 6; P14, 4 versus 5; P15, 4 versus 6; P16, 5 versus 6.
and pro-atherogenic metabolic, inflammatory, and immunological conditions and therefore should improve and prevent cardiovascular damage [21]. To our knowledge, no previous studies showed the changes in PLR and NLR during and after treatment of HCV by DAAs (sofosbuvir and daclatasvir) in patients with HCV-related thrombocytopenia. There was thrombocytopenia before starting treatment with DAAs with platelet mean±SD of 82.25±23.64. HCV-related thrombocytopenia may be caused by bone marrow suppression, thrombopoietin deficiency owing to liver affection, and aberrations of the immune system, resulting in anti-platelet antibodies and/or immune-complexes formation that remove platelets prematurely [27]. Binding between HCV and human CD81 receptor on the platelet membrane resulting in autoantibody production against this complex is another possible mechanism [28]. It is also hypothesized that HCV may directly affect megakaryocytes, thus causing their depletion [29]. Our results showed initial decrease in platelets count at 4 weeks (77.01±18.58) then platelet increase at 12 weeks (90.84±18.86) and then start to decrease again to reach lower level at 36 weeks (SVR-24) (80.26±18.67). This disagreed with Hussein [30], who found increase platelet count after eradication of HCV by DDAs. With eradication of the viral load, the antibodies disappear and platelets increase. This agreed with Lee et al. [31] who found exacerbation of thrombocytopenia after eradication of HCV by DDAs. Immune alteration following eradication of HCV and subsequent modification of autoimmunity could affect course of immune thrombocytopenia associated with HCV infection. Both PLR and NLR initially increase at 4 weeks after start of treatment, then both significantly decrease to reach lowest level at 36 weeks (SVR-24) (60.26±12.67 for PLR and 1.33±0.24 for NLR). The effect of HCV eradication on PLR and NLR was shown by Meng et al. [26] who showed that the PLR of the HCV cleared group was significantly higher than that of the HCV untreated group and HCV uncleared group, but for NLR, no statistically significant change was found among the different groups HCV untreated, HCV uncleared, and HCV cleared. Meng et al. [26] did not use DAAs but used peg-interferon plus ribavirin. As HCV produces systemic inflammation, which can result in increase in the development of atherosclerosis, insulin resistance, and cardiovascular disorders, and as both PLR and NLR are considered systemic inflammatory biomarkers, they can reflect the inflammatory and immune status during treatment with DDAs and up to 24 weeks after eradication of HCV. The DDAs target specific nonstructural proteins of HCV and result in disruption of viral replication [14]; moreover, they do not directly interfere with other conditions that potentially affect atherosclerosis or cardiovascular diseases and therefore the changes that occur in PLR and NLR after end of treatment are owing to HCV eradication. Our results found initial increase in both NLR and PLR at 4 weeks, which may reflect initial increase of systemic inflammation associated with immune reconstitution which occur initially after HCV clearance with DDAs; then PLR and NLR start to decrease to reach lowest level at 36 weeks (SVR-24), which would reflect the decreased systemic inflammation achieved after HCV eradication by DDAs in patients with HCV-related thrombocytopenia and so decreasing the risk of development of atherosclerosis, IR, and cardiovascular diseases.

Conclusion
PLR and NLR are both decreased after HCV eradication by DDAs in HCV-infected patients with thrombocytopenia, suggesting improvement of the HCV–associated systemic inflammation.

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Conflicts of interest
There are no conflicts of interest.

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