Platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio and monocyte-to-HDL cholesterol ratio as helpful biomarkers for patients hospitalized for deep vein thrombosis

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Abstract. There is an increased interest for novel biomarkers in order to improve the diagnostic accuracy for deep vein thrombosis (DVT). Moreover, the link between inflammation and venous thromboembolism has attracted increasing research interests. The present study aimed to evaluate the role of the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-high-density lipoprotein cholesterol ratio (MHR) as biomarkers for acute DVT. For this purpose, 300 consecutive patients who were hospitalized were considered; 33 patients out of the 300 were admitted for acute DVT of the lower limbs. The PLR, NLR and MHR, as well as the acute phase inflammation markers (leukocytes, neutrophils, C-reactive protein and fibrinogen) were measured. The patients with DVT exhibited significantly higher levels of PLR, NLR and MHR compared to those without DVT (P<0.001). Simple binary linear regression analysis (without confounding factors) between the NLR, PLR and MHR highest quartile and DVT revealed an odds ratio of 3.149 (P=0.01) for PLR, and an odds ratio of 4.191 (P=0.001) for MHR. Following the correction for the main confounding factors, PLR maintained a significant association with DVT (odds ratio, 3.379; P=0.007) and MHR maintained a stronger significant association with DVT (odds ratio, 4.378; P=0.001). It was thus hypothesized that the assessment of PLR and MHR, but not of NLR may help clinicians to improve the laboratory evaluation in elderly hospitalized patients with suspected DVT.

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Introduction

Deep vein thrombosis (DVT) of the lower limbs is often clinically silent (1), and the lack of specificity and sensitivity of symptoms and signals often lead to an ambiguous diagnosis. Furthermore, the incidence of venous thromboembolism (VTE) markedly increases in individuals >45 years of age, and the risk of developing VTE in the elderly population (>85 years) is up to 8 events per 1,000 (2). In order to diagnose DVT, a pre-test probability calculation associated with the assay of selected biomarkers is usually considered. D-dimer is the major available biomarker; however, despite the appropriate use of this assay, uncertainties in the diagnosis of DVT frequently persist (3). Thus, there is a need for the identification of novel biomarkers which are able to identify high-risk patients in order to achieve objectives, such as early anticoagulation or avoid diagnostic tests (i.e., ultrasound or computerized tomography) for low-risk patients (4). The close link between inflammation, coagulation imbalance and VTE has led researchers to focus on the role played by blood cells, particularly leukocytes and platelets (5-8). The platelet-to-lymphocyte ratio (PLR), the neutrophil-to-lymphocyte ratio (NLR) and the monocyte-to-high-density lipoprotein (HDL) ratio (MHR) are also evaluated. The PLR is the ratio between the absolute count of platelets and lymphocytes. The NLR is calculated by dividing the number of neutrophils (increased in inflammatory events) by the number of lymphocytes and is used as

a marker of subclinical inflammation. The MHR has been reported as a new indicator of inflammation and oxidative stress (6,9-11). Although some studies have been performed to evaluate the role of PLR, NLR and MHR in DVT (12-14), no concrete results have yet been obtained, particularly in elderly hospitalized patients. Therefore, the aim of the present study was to assess the levels of NLR, PLR and MHR in elderly hospitalized patients with DVT in order to assess the efficacy of these markers in the diagnosis of DVT.

Patients and methods

Study population. The present study enrolled 300 consecutive patients, aged >70 years, who were hospitalized in the General Hospital 'Nuovo Ospedale Garibaldi' of Catania, Italy during the period between January and December, 2020 Of the enrolled patients, 33 were admitted for DVT of the lower limbs, and 267 for medical reasons other than DVT (used as the controls). None of the hospitalized patients were infected by SARS-Cov2; all the patients enrolled were screened for SARS-Cov2 when they presented to the first aid room of the hospital and then hospitalized only if the PCR test was negative. The present study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Garibaldi Hospital (Catania, Italy; approval no. 23/2016/CECT2). Patients were informed about the study, and were first requested to provide their informed content. All patients provided their verbal content to be included in the study. DVT of the lower limbs was diagnosed according to the latest guidelines (15), using a B-mode ultrasound (US) system (Esaote Mylab 5) equipped with a 7-12 MHz linear probe. Hospitalized patients were subjected to the US examination at the time of admission to the medical department. Where necessary, and in relation to the clinical status of the patient, the screening was supplemented with a computed tomography angiography (CTA) of the chest to exclude the concurrent presence of pulmonary embolism. To avoid confounding data in relation to the aim of the study, patients with malignancies, inflammatory diseases, autoimmune diseases, hematologic diseases, hepatic insufficiency, chronic kidney disease, acute coronary syndrome, decompensated type 2 diabetes, and patients who had received immunosuppressive drugs or corticosteroids in the last month or any other drug that can affect the platelet, lymphocyte or monocyte counts and/or HDL cholesterol levels were excluded. Upon admission, characteristics such as sex, age, weight, body mass index (BMI; defined as the body mass divided by the square of the body height (kg/m^2), as well as the presence of the main cardiovascular risk factors (diabetes, arterial hypertension, cigarette smoking, dyslipidemia) were recorded, based on the clinical examination, and laboratory tests performed. A complete medical history made it possible to define all other disorders which the enrolled patients were suffering from, active or inactive, which were treated by continuing the medications and doses already practiced, intervening with appropriate modifications if deemed necessary by the treating clinician in relation to the patient's clinical evolution.

Biochemical assessments. All biochemical assessments were performed in the central laboratory of General Hospital Nuovo Ospedale Garibaldi of Catania, Italy by using their usual methods in determining measurements. Blood samples of all patients enrolled were collected upon hospital admission. Complete blood count was determined using a hematology analyzer (DX 800, Beckman Coulter, Inc.), serum glucose and blood urea nitrogen levels were measured using the Architect system (Glucose: kit ref 3L82-42, Abbott Pharmaceutical; urea nitrogen: kit ref 04T1220, Abbott Pharmaceutical), creatinine levels were measured using MULTIGENT Creatinine (Enzymatic) Liquid assay (kit ref 8L24-41, Abbott Pharmaceutical); total cholesterol was measured using Cholestech LDX™ System, (kit ref 04S9230, Abbott Pharmaceutical); low-density lipoprotein cholesterol (LDL-C) and HDL cholesterol (HDL-C) levels were measured using kits from Abbott Pharmaceutical (Ultra HDL, kit ref 3K33-22); triglycerides were measured using the Triglyceride kit ref 7D74-22, Abbott Pharmaceutical); high-sensitivity C-reactive protein (hs-CRP) levels were measured using a respective kit (CRP VARIO, kit ref 6K26-30, Abbott Pharmaceutical); the erythrocyte sedimentation rate (ESR) was measured using the VES MATIC CUBE instrument (Diesse) and fibrinogen levels were determined using a respective kit (Q.F.A. Thrombin-bovine, kit ref 0020301700, IL Instruments). The cell count was determined using flow cytometry by the laboratory staff of the aforementioned hospital experienced in the method. PLR was calculated by the platelet count ($x10^3$/l)/total lymphocyte count ($x10^3$/l). The NLR was calculated by the neutrophil count ($x10^3$/l)/total lymphocyte count ($x10^3$/l) and the MHR was calculated by the monocyte count ($x10^3$/l)/HDL-C (mg/dl).

Statistical analysis. Continuous variables are presented as the mean ± standard deviation. Categorical variables are expressed as a percentage (or frequency). The independent-samples t-test was used to compare differences between groups for continuous variables. The comparison of the proportion was performed using the Chi-squared test or Fischer's exact test (used when the expected frequency of the event was lower than five. To examine the statistical power in identifying patients with DVT for the variables NLR, MHR and PLR, a targeted analysis was conducted using a receiver operating characteristic (ROC) curve PLR, NLR and MHR were categorized according to the highest quartile (top quartile) of the entire statistical collective (NLR >5.7; NLR >237.5; MHR >50.0). This subdivision was subsequently used to conduct multivariate logistic regression analysis with the aim of demonstrating that higher values of PLR, NLR and MHR are independently associated with DVT by introducing confounding variables into the model. The following confounders were considered in the analysis: Serum creatinine, creatinine clearance calculated through the Chronic Kidney Disease Epidemiology Collaboration (CKD_EPI) formula, ESR, CRP, smoking, age. A two-tailed P-value <0.05 was considered to indicate a statistically significant difference. Statistical analyses were performed using IBM SPSS Statistics 25 (SPSS, Inc.).

Results

The main clinical and laboratory data of the study population are presented in Table I. The neutrophil, lymphocyte and

Table I. Main characteristics of the study population.

Variable	Controls (n=267)	Patients with DVT (n=33)	P-value[a]
Age, years	81±7	82±8	0.516
Male sex, n (%)	118 (44.2)	13 (39.4)	0.370
Body mass index, kg/m^2	28.2±5.0	27.5±5.0	0.486
eGFR[b], ml/min/1.73 m^2	61±27	61±32	0.943
Ankle-brachial index	1.05±0.18	1.08±0.31	0.442
Diabetes, n (%)	86 (32.2)	6 (18.2)	0.070
COPD, n (%)	34 (12.8)	4 (12.1)	0.937
Coronary artery disease, n (%)	28 (10.5)	7 (21.2)	0.070
AF, n (%)	46 (17.2)	7 (21.2)	0.359
Cerebrovascular disease, n (%)	20 (7.5)	4 (12.1)	0.356
Hypertension, n (%)	148 (55.4)	19 (57.6)	0.815
Dyslipidemia, n (%)	123 (46.1)	18 (54.5)	0.357
Smoking, n (%)	100 (37.5)	13 (39.4)	0.828
Heart failure, n (%)	27 (10.1)	3 (9.1)	0.804
Hepatic steatosis, n (%)	51 (19.1)	6 (18.2)	0.894
Neutrophil count,	4,832±1,825	5,239±2,049	0.234
Lymphocyte count,	1,620±689	1,144±641	<0.001
Platelet count, 10^3	220±90	282±102	<0.001
NLR	3.59±2.65	6.44±7.28	<0.001
PLR	167±109	333±231	<0.001
MHR	24.8±13.3	34.5±12.4	<0.001
ESR (1st h)	30.4±18.6	40.8±19.4	0.003
CRP, log (mg/l)	0.11±0.53	0.52±0.32	0.008
Fibrinogen (mg/dl)	366±107	410±116	0.027

Data are presented as the mean ± SD or as numbers and percentages. [a]The independent-samples t-test was used to compare differences between groups for continuous variables. The comparison of the proportion was performed using the Chi-squared test or the exact Fischer's test (used when the expected frequency of the event was lower than five. Numbers in bold font indicate statistically significant differences (P<0.05). [b]The glomerular filtration rate was estimated using the CKD-EPI formula. COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; MHR, monocytes-to-high-density lipoprotein cholesterol ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Table II. Simple binary linear regression analysis (without confounding factors).

Variable	B value	Standard error	Wald value	P-value	Odds ratio	95% CI EXP(B) inf	95% CI EXP(B) sup
NLR	0.357	0.445	0.643	0.423	1.429	0.597	3.422
PLR	1.147	0.445	6.641	0.01	3.149	1.316	7.536
MHR	1.433	0.428	11.201	0.001	4.191	1.811	9.699

PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; MHR, monocytes-to-high-density lipoprotein cholesterol ratio.

platelet counts were found to be 5,239±2,049, 1,144±641 and 282±102 in the patients with DVT vs. 4,832±1,825, 1,620±689 and 220±90x10^3 in the controls (no DVT), respectively. The difference was statistically significant for the lymphocyte and platelet counts, but not for the neutrophil count. The ESR was significantly higher in the patients with DVT (40.8±19.4) compared to the controls with no DVT (30.4±18.6) (P=0.003). The CRP levels were significantly higher in the patients with DVT (0.52±0.32 mg/l) than in the controls (0.11±0.53 mg/l) (P=0.008). Fibrinogen levels were also significantly higher in the patients with DVT (410±116 mg/dl) than in the controls (366±107 mg/dl) (P=0.27). The NLR, PLR and MHR were significantly increased in the patients with DVT compared with the controls with no DVT (P<0.001).

The results of the simple binary linear regression analysis (without confounding factors) between the NLR, PLR and MHR highest quartile and DVT are presented in Table II. The PLR odds ratio was 3.149 (P=0.01); MHR was found

Table III. Simple binary linear regression analysis (with confounding factors).

Variable	B value	Standard error	Wald value	P-value	Odds ratio	95% CI EXP(B) inf	95% CI EXP(B) sup
NLR	0.311	0.468	.441	0.507	1.365	0.545	3.416
PLR	1.218	0.455	7.151	0.007	3.379	1.384	8.249
MHR	1.477	0.452	10.693	0.001	4.378	1.807	10.607
Creatinine	-0.044	0.142	0.098	0.755	0.957	0.724	1.264
GFR	0.003	0.009	0.157	0.692	1.003	0.987	1.020
ESR	0.000	0.013	0.000	0.985	1.000	0.975	1.026
CRP	-0.007	0.059	0.012	0.911	0.993	0.886	1.114
Fibrinogen	0.001	0.002	0.387	0.534	1.001	0.997	1.005
Cigarette smoking	0.464	0.432	1.151	0.283	1.590	0.681	3.712
Age, years	0.008	0.032	0.064	0.800	1.008	0.946	1.074

The glomerular filtration rate was estimated using the CKD-EPI formula (30). PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; MHR, monocytes-to-high-density lipoprotein cholesterol ratio; GRF, glomerular filtration rate; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

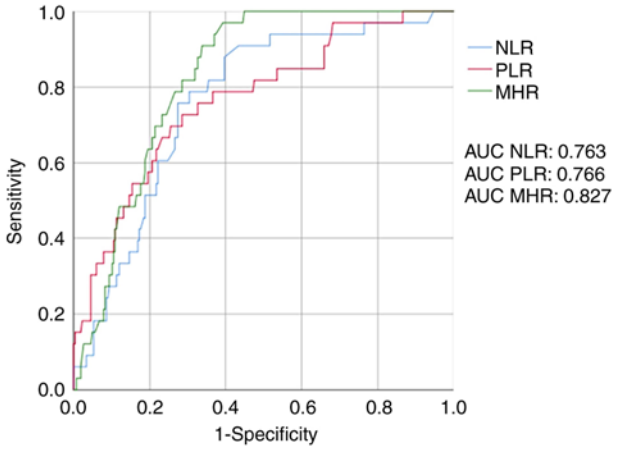

Figure 1. Receiver operating characteristic curves for PLR, NLR and MHR. PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; MHR, monocyte-to-high-density lipoprotein cholesterol ratio; AUC, area under the curve.

to have a higher association with DVT and an odds ratio of 4.191 (P=0.001). No significant association was found for NLR (odds ratio, 1.429; P=0.423).

The results of the simple binary linear regression analysis between NLR, PLR and MHR highest quartile and DVT are presented in Table III. In this analysis, the following confounding factors were taken in into account: Creatinine, GFR, ESR, CRP, fibrinogen, cigarette smoking and age. Following the correction, PLR maintained a significant association with DVT diagnosis, with an odds ratio of 3.379 (P=0.007) and MHR maintained a more significant association with DVT, with an odds ratio of 4.378 (P=0.001). The ROC curves for the evaluation of the accuracy and the performance of NLR, MLR and MHR in predicting the diagnosis of DVT is illustrated in Fig. 1. The area under the curve (AUC) for NLR was 0.763 (95% CI, 0.686-0.840), the AUC for PLR was 0.766 (95% CI, 0.679-0.853) and the AUC for MHR was 0.827 (95% CI, 0.775-0.879).

Discussion

The present study analyzed a sample of 300 hospitalized patients, 11% of whom were diagnosed with DVT patients using the US method. The findings presented herein suggest that the PLR, and for the first time (to the best of our knowledge) the MHR (but not the NLR), may be used as effective biomarkers for improving the diagnostic process for patients suspected of having DVT. The PLR and MHR were found to be independently associated with the thrombotic event, even when considering the main confounding factors. It is well established that the increased value of PLR, a biomarker which is more informative than the platelet count alone, is associated with a worse prognosis in several types of malignancies. Moreover, the PLR has been found as an independent predictor of mortality in patients with ST-segment elevation, myocardial infarction and chronic ischemic heart disease. It is also associated with the progression of atherosclerotic damage (5,6,8). The NLR, on the other hand, is an established marker of subclinical inflammation; high NLR values are considered as a negative prognostic marker in a number of arterial vascular disorders, indicating a higher level of systemic inflammation (5,6,8). The MHR has been reported as cost-effective and highly predictive marker in several cardiovascular diseases (7). Only a few studies to date have evaluated these promising biomarkers with regards to DVT, despite substantial pathophysiological premises suggesting their potential role. Artoni *et al* (13) performed a large population study aiming to investigate the PLR and NLR as risk factors for VTE in patients with venous thromboembolism or cerebral veins thrombosis (CVT) and demonstrated a lack of an association between the NLR and PLR, and the risk of venous thrombotic diseases, although they reported that high PLR values were associated with the risk of provoked CVT (odds ratio, 2.65). The results of the present study are partly in contrast to these, although it should be noted that the study by Artoni *et al* (13) enrolled non-acute outpatients who were referred for thrombophilia screening after a first, symptomatic, objectively confirmed episode of

VTE or CVT. In addition, the mean age of the subjects with DVT was 47.9 years, and the patients with CVT were even younger (mean age, 36.3 years). These are therefore research contexts and populations that are hardly comparable, and the results may not necessarily be in conflict with each other, assessing different periods and populations. To the best of our knowledge, the present study, for the first time, suggests a possible role of MHR as a biomarker in DVT in hospitalized and elderly patients. A previous study (15) evaluated the potential predictive value of MHR in DVT. That study enrolled 853 patients undergoing primary total joint arthroplasty. That study reported a significant association between pre-operative MHR and DVT (odds ratio, 10.43; P=0.008). A notable finding of that study concerning the MHR, a putative marker of systemic inflammation, underscores the putative role that these new biomarkers focusing on platelet activity and on systemic inflammation can play in the screening and diagnostic flowchart for DVT.

The crosstalk between inflammation, platelet activity and thrombin generation has been largely examined; inflammation affects the initiation and propagation of activated coagulation, also upregulating physiological anticoagulants (i.e., antithrombin, protein C system and tissue factor pathway inhibitor, and the inhibition of fibrin removal) (14,15). The association between inflammation and activated coagulation is a complex pathway and contact between the cells of the bloodstream (leukocyte and platelets) with the altered endothelial membrane is crucial for the thrombotic process. It is known that due to venous stasis, the venous wall undergoes hypoxia and oxidative stress, which finally leads to the dysfunction of the endothelial barrier. A dysfunctional endothelium expresses the adhesion receptors, leading to the recruitment of bloodstream cells, particularly leukocytes and platelets (16). In addition, the pro-coagulative extrinsic pathway initiated by exposure to tissue factor leads to the release of activate coagulative factor XII from granulocytes, and thus the hypercoagulative pathway is activated. Thus, both local and systemic inflammation may be considered as driving factors for the trigger and development of venous thrombosis (2,3,17-19), overlapping the other potential acute or chronic risk factors (19).

Hospitalized patients, particularly the elderly, often suffer from comorbidities and disorders of the venous peripheral circulation (including venous stasis, varicose veins, skin damage, ulcers). Thus, this is a setting of patients exhibiting a chronic low grade of inflammation, coagulation abnormalities and transient (i.e., bed rest) or lifelong predisposing factors for the risk of DVT (2,20,21). It should be noted that aged and hospitalized patients have a 8-fold higher incidence of DVT compared to the general population (2,22). The present study indicated that in the specific clinical setting of hospitalized patients with DVT, a more active immune-inflammatory background can be identified diversely in patients without DVT, as shown by the higher values of NPL, PLR and MHR in patients with DVT compared with those without DVT. In clinical practice, this would confirm the pathophysiological assumptions previously outlined (2,20,21). It is largely approved that none of the clinical signals (swelling, pain, redness, etc.) are specific or sensitive for the diagnosis of DVT. In the present study, high levels of PLR and MHR were also found to be predictors of DVT, independently from the main confounders, also exhibiting good performance as biomarkers of DVT, as evidenced from the analysis of the ROC curves that were created. The finding of the lack of the predictive capacity of NLR for DVT deserves to be carefully analyzed. Many studies, the vast majority retrospective, have demonstrated the promising predictive capability of the PLR for VTE onset, poor prognosis and mortality (23-27). However, the results obtained have not yet been fully validated in clinical settings. A few studies, beyond ours, have shown no significant association between NLR and DVT (13), NLR and pulmonary embolism (PE) (28) and NLR and mortality after an episode of PE (29).

The present study has certain limitations which should be mentioned. It remains to be clarified whether the elevated values of PLR or NLR are causally related to thrombosis or whether they merely express the acute inflammatory activity occurring in the vascular event. However, the results of the present study demonstrate the different inflammatory pathways between patients with the DVT and those without. The results of the study suggest that clinicians need to be aware of a specific setting of hospitalized patients with high levels of the aforementioned biomarkers in order to monitor their risk of developing DVT, even though the US data are negative or they do not exhibit a clinical picture. The present study tried to limit the possible confounders by excluding all diseases or drugs that can alter the indices considered and by correcting the analysis for the main confounders. However, the extent to which the acute phase response may alter the increase in PLR or NLR or whether their increase is actually an expression of a predisposing pro-inflammatory background needs to be further elucidated.

In conclusion, the results of the present suggest that the assessment of PLR and MHR, but not NLR can help clinicians to improve the laboratory evaluations of hospitalized patients suspected of having DVT, particularly in aged patients and those with co-morbidities. The PLR and MHR indexes may be helpful tools for screening inflammatory levels in individuals and/or in patients potentially prone to VTE events. Easy and repeatable blood biomarkers may help to screen inflammatory levels as crucial agents for determining the risk of developing DVT, particularly in the setting of aged individuals or hospitalized patients.

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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.

Authors' contributions

SS was involved in the design of the study, in recruiting the patients, and in writing and revising the manuscript. GB, AA, CM and GD were involved in recruiting the patients and obtaining

patient data, and in revising the manuscript. MR and DDR were involved in the statistical analysis, and in writing and revising the manuscript. EP was involved in the statistical analysis and in revising the manuscript. SSS was involved in the design of the study, in recruiting the patients, and in writing and revising the manuscript. All authors have read and approved the final manuscript. SS and SSS confirm the authenticity of all the raw data

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Garibaldi Hospital (Catania, Italy; approval no. 23/2016/CECT2). Patients were informed about the study, and were first requested to provide their informed content. All patients provided their verbal content to be included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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