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Evaluation of the relationship between monocyte to high-density lipoprotein cholesterol ratio and thrombus burden in patients with deep vein thrombosis

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SUMMARY

OBJECTIVE: The purpose of this study was to evaluate monocyte count and high-density lipoprotein cholesterol levels and their ratio (monocyte/high-density lipoprotein ratio) in patients with deep venous thrombosis as well as to determine whether this ratio at the time of diagnosis can be an indicator of thrombus burden in terms of thrombus location in deep venous thrombosis.

METHODS: We retrospectively analyzed the patient's diagnosis of deep venous thrombosis confirmed with venous Doppler ultrasound, using a database query for outpatients between 2018 and 2022. Of 378 patients included, blood count results at the time of diagnosis were available for 356. We recruited 300 age- and sex-matched patients with appropriate blood counts, without a diagnosis of deep venous thrombosis, as the control group, by querying the outpatient clinic database. The monocyte/high-density lipoprotein ratio was computed from the ratio of monocyte count to high-density lipoprotein-C. Patients were categorized based on the level of thrombus and the number of vein segments involved as evidenced by Doppler ultrasound findings.

RESULTS: The serum level of monocyte/high-density lipoprotein ratio was significantly higher in the patient group compared to the control group ($p<0.01$). Patients with proximal deep venous thrombosis had a higher mean monocyte/high-density lipoprotein ratio (19.6±5.1 vs. 17.1±5.5; $p<0.01$) than patients with distal deep venous thrombosis. Monocyte/high-density lipoprotein ratio increased with the number of vein segments involved ($p<0.01$).

CONCLUSION: Monocyte/high-density lipoprotein ratio is significantly elevated in patients with deep venous thrombosis when compared to the control group. Monocyte/high-density lipoprotein ratio levels were correlated with disease burden reflected by thrombus location and the number of vein segments involved in deep venous thrombosis patients.

KEYWORDS: Venous thrombosis. Cholesterol, HDL. Monocytes.

INTRODUCTION

Deep venous thrombosis (DVT) is the third leading vascular problem globally[1], and evidence of its association with inflammation is increasing[2-6]. In patients with acute DVT, several inflammatory markers were shown to be at increased levels[6-8]. Whether the relationship with increased inflammation is causal to or a result of DVT is under dispute, but it is apparent that a state of increased inflammation is present in patients with DVT at the time of diagnosis.

In current clinical practice, high-sensitivity C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the most widely used inflammatory markers[9,10]. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which are calculated from the white blood cell count, are reported to be novel inflammatory biomarkers in patients with venous thrombosis[11]. Decreased high-density lipoprotein cholesterol (HDL-C) levels and increased monocyte counts were also found to be associated with inflammation, and the monocyte to HDL-C ratio (MHR) was suggested to be used as a novel inflammatory biomarker[12,13]. HDL-C has a protective effect against low-density lipoprotein (LDL) oxidation and monocyte activation[14-16]. MHR was reported to be a new cardiovascular prognostic marker in chronic kidney disease[13]. The MHR is also associated with coronary artery disease (CAD) severity and complexity in stable CAD[17].

To the best of our knowledge, no study has evaluated the association of MHR with venous thrombotic events. Therefore, the objective of this study was to determine whether MHR, calculated at the time of diagnosis, can be an indicator of thrombus burden in terms of thrombus location and the number of vein segments involved in DVT patients.

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METHODS

We retrospectively analyzed patients with a diagnosis of DVT, using a database query for outpatients at our referral center between 2018 and 2022. This study was approved by the hospital's review board, and the study was carried out in accordance with the Declaration of Helsinki. Patients whose diagnosis of acute DVT was confirmed with venous Doppler ultrasound in the records were included. Patients with known prior DVT or signs of chronic thrombus on Doppler ultrasound screening were excluded. Of 378 patients included, blood count results at the time of diagnosis were available for 356. We recruited 300 age- and sex-matched patients with appropriate blood counts, without a diagnosis of DVT, as the control group, by querying the outpatient clinic database (Figure 1). The basic demographic and clinical characteristics (i.e., age, sex, hypertension, diabetes mellitus, smoking, and heart diseases) were recorded. Evaluation of the association of MHR with DVT at the time of diagnosis was performed for patients with blood counts at the index visit.

The standard ultrasound screening protocol included all deep and superficial lower extremity veins, including the external iliac veins, with compression, followed by a color and spectral Doppler ultrasound evaluation of filling and flow patterns. Higher portions of the external iliac vein and the common iliac vein were evaluated as much as permitted by the patient's anatomy.

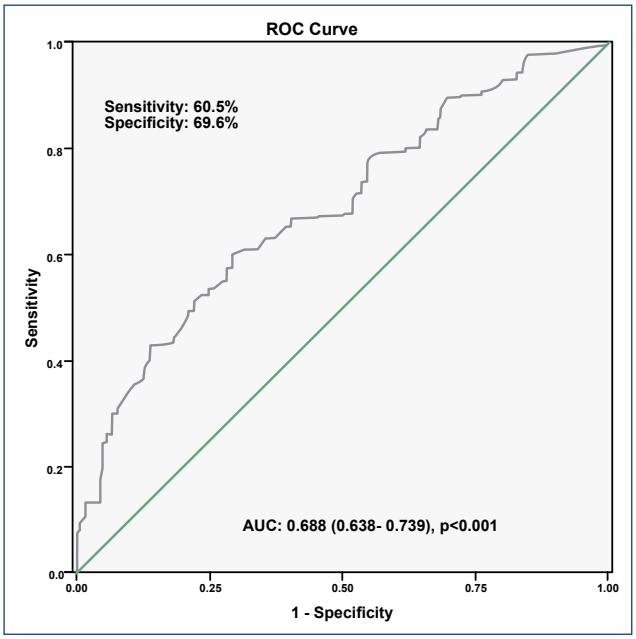

Figure 1. Receiver operating characteristic curve of the monocyte to high-density lipoprotein ratio for predicting thrombus localization in patients with deep venous thrombosis. AUC: area under the curve; CI: confidence interval.

MHR at the time of diagnosis was calculated for each patient from standard blood cell counts. Patients were grouped based on the location of venous thrombus visualized by Doppler ultrasound as iliac, femoral, popliteal, or crural. When thrombus was located in more than one segment, categorization followed the highest of the segments. Crural veins included anterior tibial, posterior tibial, and peroneal veins along with gastrocnemius and soleal veins. Groups were compared for MHR of corresponding patients. Thromboses were categorized as distal DVT in the crural or popliteal veins and as proximal DVT in femoral or iliac veins to facilitate receiver operating characteristic (ROC) curve analysis used to determine the discriminatory ability of MHR for thrombus location. The extent of thrombus was evaluated with the number of vein segments with thrombus detected by Doppler ultrasound in an additive fashion.

Statistical methods

The SPSS 21.0 for Windows was used for statistical analyses (SPSS, Chicago, IL). Besides descriptive statistics, Student's t-test and one-way analysis of variance (ANOVA) were used to compare groups for quantitative data. The Tukey test was used for post hoc analysis of ANOVA results. ROC curves were used to determine a cutoff value for variables. Significance was set at $p<0.05$.

RESULTS

As a result of our database query, 378 patients were identified with a diagnosis of DVT between 2018 and 2022 confirmed with venous Doppler ultrasound. Of 378 patients included, blood count results at the time of diagnosis were available for 356. We recruited 300 age- and sex-matched patients with appropriate blood counts, without a diagnosis of DVT, as the control group, by querying the outpatient clinic database. The baseline demographic and laboratory features of both two groups are given in Table 1. Both study groups were similar with regard to age, sex, BMI, diabetes mellitus, hypertension, previous history of CAD, and smoking habits. Serum levels of MHR were significantly higher in the patient group when compared to the control group ($p<0.01$).

Patients were separated into four groups (i.e., iliac, femoral, popliteal, and crural) based on the anatomic location of venous thrombus. MHRs of 356 patients with blood count results were calculated and compared across groups. The results of group comparisons are given in Table 2A. For MHR, there was a statistically significant difference between groups as determined by one-way ANOVA ($p<0.010$). To evaluate the discriminatory value of MHR for thrombus location, the four anatomic

locations were classified as proximal (iliac and femoral) or distal (popliteal or crural). MHR was then compared between proximal and distal DVT classifications. Proximal DVT was found to have higher means of MHR than that of distal DVT (p<0.010) (Table 2A). MHR was compared in terms of the number of segments involved in DVT. MHR in those with three and four segments involved was observed to be higher than those with one and two segments involved (Table 2B). We used ROC curves to investigate whether MHR (Figure 1) could be used to predict thrombus localization. The area under the curve is 0.688 (95% confidence interval, 0.641–0.733; p<0.001). The cutoff value of MHR for the diagnosis of proximal DVT was 16.8 with a sensitivity of 60.5% and a specificity of 69.6%.

DISCUSSION

Our study showed that MHR is significantly elevated in patients with DVT when compared to the control group. Therefore, elevated MHR levels may be a useful marker for the assessment of DVT development.

There is growing evidence that inflammation plays a role in the pathophysiology of DVT[18]. Elevated levels of CRP and

Table 1. Baseline demographic and laboratory characteristics of both patient and control groups.

Parameters	Patient group (n=356)	Control group (n=300)	p-value
Demographic parameters			
Age, years	55.14±9.4	54.71±9.5	0.52
Gender (male/female)	207/149	168/132	0.62
Hypertension, n (%)	78 (21.9%)	70 (23.3%)	0.73
Diabetes mellitus, n (%)	32 (8.9%)	33 (11.0%)	0.41
Smoker, n (%)	155 (43.5%)	126 (42.0%)	0.80
History of CAD, n (%)	49 (13.7%)	45 (15.0%)	0.69
Laboratory parameters			
Monocyte (×10^9/L)	604±198.6	420.4±120.1	**<0.01**
HDL (mg/dL)	33.9±8.2	43.3±11.9	**<0.01**
LDL (mg/dL)	116±31.6	123.1±37.2	0.34
TG (mg/dL)	140±75.1	131±47.5	0.21
Total cholesterol (mg/dL)	195.2±42.4	191.3±41.0	0.28
MHR	18.3±4.6	10.4±5.2	**<0.01**

Bold indicates statistically significant p-values.

Table 2A. Monocyte to high-density lipoprotein-C ratio based on the thrombus location.

Ratio	Iliac (n: 56)	Femoral (n: 185)	Popliteal (n: 92)	Crural (n: 23)	p-value
MHR	19.8±5.4*	19.2±4.9**	17.6±4.4***	17.3±5.8	<0.010
	Proximal (n: 241)		Distal (n: 115)		
MHR	19.6±5.1		17.1±5.5		<0.010

*Iliac vs. Femoral p<0.05; and vs. Popliteal and vs. Crural p<0.010; **Femoral vs. Popliteal and vs. Crural p<0.010; ***Popliteal vs. Crural p>0.05.

Table 2B. Monocyte to high-density lipoprotein-C ratio based on the number of affected venous segments.

	Number of segments with thrombus				p
	1	2*	3**	4***	
MHR	17.8±4.3	17.7±4.7	19.4±5.8	20.1±5.2	<0.010

***4 vs. 3 p<0.05 and vs. 2 and vs. 1 p<0.010; **3 vs. 2 and vs. 1 p<0.05; *2 vs. 1 p>0.05.

interleukin (IL)-6 at the time of diagnosis have been linked to increased inflammation, DVT severity, and thrombus location at the femoral and iliac sites[6]. Low levels of CRP were also found to be useful as a negative predictor in DVT[19], and plasma levels of IL-6, IL-8, and CRP were higher in patients with newly diagnosed DVT[20]. The release of tissue factors caused by inflammatory cytokines has been linked to the thrombosis cascade's initial event, which is vein wall inflammation[2]. Increased levels of inflammatory mediators following surgery can also be blamed for the higher frequency of VTE during the immediate postoperative period. This could also be the reason why DVT is linked to conditions including sepsis, CMV, influenza, chlamydia, and other infections, as well as inflammatory bowel disease, obesity, rheumatological disorders, and cystic fibrosis[2,21]. All these pathological processes and other well-known risk factors of DVT are associated with an inflammatory state[3]. As inflammation is involved in both thrombus formation and its clearance, it is still unclear whether this link is causal or a consequence[2].

Moreover, MHR was investigated as a new inflammation biomarker and considered superior to subtypes of white blood cells (WBCs) in patients with cardiovascular and cerebrovascular diseases[12,13,22-26]. Monocytes are the indicators of inflammatory reactions because they are responsible for the secretion of proinflammatory and prooxidant cytokines[27]. On the contrary, HDL cholesterol has antioxidant and anti-inflammatory effects such as reducing macrophage accumulation, inhibiting the transmigration of monocytes, increasing the expression of nitric oxide synthase in endothelial tissues, and protecting the endothelial cells[28].

Based on our findings, MHR increased in DVT patients with a higher location of thrombus. Patients with iliac or femoral vein thromboses had statistically higher MHR compared with patients with distal DVT. Differentiation cannot be made as to whether the environment of increased inflammation was present before the onset of the disease and caused the thrombus or whether it was a response to the thrombus forming within the vein. Regardless of the direction of the relationship, the findings point to an elevated level of inflammation with a higher thrombus location in DVT. Similarly, our results showed an increase in MHR, albeit partially proportional to the number of vein segments with thrombus, signifying an increased inflammation associated with the extent of thrombus. Other inflammatory markers including D-dimer, soluble P-selectin, and CRP were investigated by Vandy et al.[29], who demonstrated an increase in these biomarkers with the extent of thrombus in the vein segments of the lower extremity. These findings together suggest an elevated state of inflammation with increased thrombus severity.

MHR is a marker of inflammation that is inexpensive, ubiquitous, and easy to interpret. We performed an ROC curve analysis to assess whether the increased MHR value at the time of diagnosis can provide predictive information for the thrombus location. The area under the curve for MHR was 0.688, and the sensitivity and specificity of the calculated cutoff scores were not sufficiently high (60.5 and 69.6%) for these values to be confidently used alone to ascertain a proximally located DVT. Further research can be conducted by combining these ratios with clinical findings or other laboratory markers to aid in patient evaluation or to guide treatment. Another direction for further clinical studies may also be to look into the relationship between these markers in the follow-up or recurrence of DVT to assess the value of MHR in directing an anticoagulation regimen and its duration.

Limitations

We did not analyze other inflammatory parameters such as ILs, CRP, and other subtypes of WBC. Our study had a retrospective single-center study design. A similar study with a prospective design can be carried out, potentially including clinical variables at the time of diagnosis, to assess the relationship of MHR with disease severity and their predictive ability.

CONCLUSION

MHR is significantly elevated in patients with DVT when compared to the control group. We found that MHR levels were correlated with disease burden reflected by thrombus location and the number of vein segments involved in DVT patients, a finding that supports the relationship between the extent of venous thrombus and increased inflammation. MHR may have diagnostic use at the bedside. Further studies are required to confirm their value.

AUTHORS' CONTRIBUTIONS

ZD: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Visualization, Writing – original draft. **GB:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Visualization, Writing – review & editing. **ŞD:** Investigation, Methodology, Visualization. **HU:** Investigation, Methodology, Visualization. **İE:** Methodology, Project administration, Supervision, Visualization, Writing – review & editing. **MY:** Methodology, Supervision, Visualization, Writing – review & editing.

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