ORIGINAL ARTICLE

Iron deficiency: a novel risk factor of recurrence in patients after unprovoked venous thromboembolism

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KEY WORDS

iron deficiency, risk factor, venous thromboembolism (unprovoked, recurrent)

ABSTRACT

INTRODUCTION Patients with unprovoked venous thromboembolism (VTE) are at high risk of recurrence; however, its predictors remain largely unknown. There is evidence that iron is implicated in the pathophysiology of thrombosis.

OBJECTIVES We aimed to investigate whether iron deficiency (ID) affects the risk of recurrence in patients after unprovoked VTE.

PATIENTS AND METHODS In this prospective cohort study, we examined 229 consecutive patients aged 65 years or younger with the first-ever episode of unprovoked VTE within 6 to 12 months prior to enrollment. The exclusion criteria were as follows: hemoglobin levels of less than 11 g/dl, heart failure, diabetes, cancer, serum creatinine levels exceeding 120 μM, and previous or current use of iron or erythropoiesis-stimulating agents, or both. ID was defined as serum ferritin levels below 30 μg/l. Recurrent VTE was recorded during a 24-month follow-up.

RESULTS ID was observed in 47 patients (21%). In a multivariate regression model, the presence of ID was associated with female sex, elevated C-reactive protein (CRP), anemia and reduced hemoglobin levels (all $P < 0.05$). In a multivariate model, the presence of ID (or low serum ferritin levels) and elevated CRP levels, but not anemia, predicted VTE recurrence during 24 months. The hazard ratio adjusted for CRP and the presence of anemia was 3.17 for ID (95% confidence interval [CI], 1.20–8.38; $P = 0.02$) and 0.64 for serum ferritin levels (95% CI, 0.43–0.94; $P = 0.02$).

CONCLUSIONS ID may represent a novel risk factor for VTE recurrence in young and middle-aged patients following an unprovoked episode.

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INTRODUCTION Deep-vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE), affect from 1 to 3 patients per 1000 persons per year.[1,2] The pathogenesis of VTE is complex and includes several hereditary and environmental factors.[3-5] In patients classified as having unprovoked VTE, the triggering factors cannot be identified despite a detailed clinical and laboratory workup.[1,4,6,7]

The risk of recurrence in patients with unprovoked VTE is substantially higher when compared with those with provoked VTE.[1,6,8] However, identification of such high-risk patients is still hardly feasible.[6,8,9]

High hematocrit levels have been demonstrated to increase the risk of VTE, probably through increased plasma viscosity and platelet reactivity.[10,11] Excessive iron stores associated with oxidative stress are suggested to favor thromboembolic events,[12,13] thus it might be speculated that iron deficiency (ID) protects against VTE. To our knowledge, there have been no prospective studies regarding the links between ID and

VTE recurrence. Therefore, we aimed to investigate whether depleted iron stores are associated with VTE recurrence in subjects after unprovoked VTE.

PATIENTS AND METHODS

Patients We recruited 229 consecutive adult outpatients with unprovoked VTE, aged 65 years or younger, referred to the Center of Coagulation Disorders in Kraków, Poland, from April 2010 to June 2012. Eligible patients had a documented diagnosis of first-ever unprovoked VTE within 12 months prior to enrollment and received oral anticoagulation of at least 3-month duration. The diagnosis of DVT was established on the basis of a positive finding on color duplex sonography, while PE was diagnosed based on a positive finding on computed tomography (CT) angiography. The exclusion criteria were as follows: provoked VTE, previous stroke or myocardial infarction, heart failure, known cancer, acute infection or known chronic inflammatory disorders, diabetes, serum creatinine levels >120 mmol/l, hemoglobin levels <11 g/dl, administration of iron, and the use of red blood cell concentrate or erythropoietin-stimulating agents either during the study or in the past. Unprovoked VTE was diagnosed in the absence of the following transient risk factors: trauma, surgery, prolonged hospitalization (3 days or more), pregnancy, childbirth, postpartum period, or the use of oral contraceptives. The University's institutional review board approved the study protocol, and all patients provided written informed consent to participate in the study.

Laboratory investigations Creatinine and blood cell counts were assayed by routine laboratory techniques. High-sensitivity C-reactive protein (hs-CRP) levels were measured using immunoturbidimetry (Instrumentation Laboratory, Lexington, Massachusetts, United States). Patients with hemoglobin levels of less than 12 g/dl in women and less than 13 g/dl in men were considered as patients with anemia.[14] Blood samples (vol/vol, 9:1 of 3.2% trisodium citrate) for coagulation parameters were drawn from an antecubital vein at 8 to 10 AM and spun at 2000 *g* for 10 minutes. The supernatant was aliquoted and stored at –80°C.

All iron status laboratory indices were assayed using the Cobas System (Roche Diagnostics, Mannheim, Germany). Serum iron levels and unsaturated iron binding capacity (UIBC) were determined using colorimetric assays with ferrozine. Total iron binding capacity (TIBC) was then calculated as a sum of serum iron levels and UIBC. Serum ferritin levels were measured by the latex-enhanced immunoturbidimetric method. In the absence of inflammation, serum ferritin can be considered a reliable proxy for the quantity of iron stores.[15,16] Transferrin saturation (T_{sat}) was calculated as a ratio of serum iron and TIBC multiplied by 100 and expressed as percentage. T_{sat} corresponds to the amount of circulating iron bound to transferrin, which reflects the quantity of iron available to metabolizing cells.[15,16] ID was defined as serum ferritin levels of less than 30 μg/l.[17]

Thrombophilia screening was performed in all patients. At the time of blood drawing, none of the subjects were receiving a vitamin K antagonist; they were switched to heparins for 2 weeks and blood was collected 12 hours after the last injection, when the international normalized ratio was less than 1.2. We assessed factor V Leiden and prothrombin G20210A mutations, antithrombin, protein C, free protein S, and factor VIII, along with markers of antiphospholipid syndrome, including lupus anticoagulant, anticardiolipin antibodies, and anti-β_2-glycoprotein I antibodies, both in immunoglobulin (Ig) G and IgM classes. Total plasma homocysteine was determined in EDTA plasma by high-performance liquid chromatography. Antiphospholipid syndrome was diagnosed based on the recommendations published in 2006.[18] All measurements were performed by technicians blinded to the origin of the samples. Intra- and interassay coefficients of variation were lower than 7%.

Clinical follow-up All participants were contacted at least twice a year by telephone or through medical visits. The endpoint of the study was symptomatic recurrent DVT diagnosed by compression ultrasound or symptomatic PE. Patients with suspected PE underwent spiral CT, followed by pulmonary angiography in the case of a high clinical probability despite normal CT scans. The minimal follow-up period was 6 months. No patient was lost to follow-up. The length of follow-up of patients was censored at 24 months.

Statistical analysis Continuous variables were tested for the normality of distribution by the Kolmogorov–Smirnov test. Those having a normal distribution were presented as a mean ± standard deviation. Otherwise continuous variables were presented as a median (interquartile range) and those variables were approximated to normality using a logarithmic ($\log_{10}$) transformation. Categorical variables were presented as numbers with percentage and were compared by the χ^2 test.

The relationships between the presence of absolute ID and its potential predictors were established using logistic regression analyses (both univariate and multivariate models). The multivariate models included the variables that were significantly associated with the presence of ID in the univariate models.

The associations between the variables and VTE recurrence during the 24-month follow-up were determined using Cox proportional hazards regression analyses (both univariate and multivariate models). The multivariate models included the variables that significantly predicted outcomes in the univariate models. In order to show the effect of ID on 24-month recurrence-free survival probabilities, Kaplan–Meier curves were constructed and compared by the Cox–Mantel log-rank test.

TABLE 1 Baseline characteristics and clinical associates of iron deficiency (as defined by serum ferritin levels <30 µg/l) in patients with unprovoked venous thromboembolism

Characteristics of the study subjects					Clinical associates of ID			
variables		values			categories/units	univariate models OR (95% CI)	multivariate model 1 OR (95% CI)	multivariate model 2 OR (95% CI)
		whole group (n = 229)	ID (+) (n = 47)	ID (–) (n = 182)[a]				
demographic and clinical characteristics								
age, y		45 ±12	43 ±12	46 ±12	1 year	0.98 (0.95–1.01)	–	–
men		116 (51)	4 (9)	112 (62)g	males vs females	0.06 (0.02–0.17)[g]	0.06 (0.02–0.20)[g]	0.04 (0.01–0.13)[g]
BMI, kg/m^2		27 ±4	27 ±4	27 ±4	1 kg/m^2	0.99 (0.92–1.08)	–	–
VTE manifestation	deep vein thrombosis[b]	167 (73)	27 (57)	140 (77)[f]	yes vs no	0.40 (0.21–0.80)[f]	0.42 (0.17–1.01)	0.50 (0.22–1.16)
	pulmonary embolism[c]	114 (50)	27 (57)	87 (48)	yes vs no	1.47 (0.77–2.83)	–	–
time since VTE event, mo		7 ±2	7 ±2	7 ±2	1 month	0.95 (0.83–1.09)	–	–
vitamin K antagonist at the time of blood collection		93 (41)	16 (34)	77 (42)	yes vs no	0.70 (0.36–1.38)	–	–
vitamin K antagonist at the time of VTE recurrence		53 (23)	12 (26)	41 (23)	yes vs no	1.18 (0.56–2.49)	–	–
family history of VTE		77 (34)	12 (26)	65 (36)	yes vs no	0.62 (0.30–1.28)	–	–
lower limb varices		53 (23)	14 (30)	39 (21)	yes vs no	1.56 (0.76–3.20)	–	–
current smoking		70 (31)	13 (28)	57 (31)	yes vs no	0.84 (0.41–1.72)	–	–
laboratory and laboratory-based characteristics								
hs-CRP, mg/l		1.9 (1.1–2.7)	2.4 (1.3–4.2)	1.8 (1.1–2.5)[f]	1 log mg/l	3.98 (1.65–9.61)[f]	2.96 (0.99–8.85)	3.27 (1.14–9.44)[e]
inherited trombophilia[d]		68 (30)	12 (26)	56 (31)	yes vs no	0.77 (0.37–1.60)	–	–
antiphospholipid syndrome[d]		25 (11)	8 (17)	17 (9)	yes vs no	1.99 (0.80–4.97)	–	–
hyperhomocysteinemia[d]		28 (12)	5 (11)	23 (13)	yes vs no	0.82 (0.29–2.31)	–	–
elevated factor VIII		53 (23)	15 (32)	38 (21)	yes vs no	1.78 (0.87–3.63)	–	–
platelet count, g/l		237 ±69	244 ±63	235 ±70	10 G/l	1.02 (0.97–1.07)	–	–
hemoglobin, g/dl		14 ±1	13 ±1	14 ±1[g]	1 g/dl	0.52 (0.37–0.71)[g]	0.53 (0.37–0.76)[g]	–
anemia[d]		22 (10)	8 (17)	14 (8)	yes vs no	2.46 (0.96–6.31)	–	8.76 (1.94–39.60)[f]
ferritin, µg/l		83 (40–179)	17 (10–21)	117 (64-207)[g]	–	–	–	–
T_{sat}, %		27 ±13	17 ±11	30 ±12[g]	–	–	–	–
T_{sat} <20%		63 (28)	31 (66)	32 (18)[g]	–	–	–	–

Data are presented as mean ± standard deviation, median (with lower and upper quartiles), or number (percentage of patients).

a *P* values for the comparison with "ID (+)" patients
b including those with concomitant pulmonary embolism (n = 52)
c including those with concomitant deep vein thrombosis (n = 52)
d as defined in the "Patients and Methods" section of the main text
e *P* <0.05; f *P* <0.01; g *P* <0.001

Abbreviations: BMI, body mass index; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; ID, iron deficiency; OR, odds ratio; VTE, venous thromboembolism; T_{sat}, transferrin saturation

TABLE 2 Prognosticators of 24-month recurrence in patients with unprovoked venous thromboembolism

Prognosticators	Categories/units	HR (95% CI)	χ^2
univariate models			
age	1 year	0.98 (0.95–1.01)	1.78
sex	males vs females	0.43 (0.18–1.04)	3.54
BMI	1 kg/m^2	1.01 (0.91–1.12)	0.04
deep vein thrombosis[a]	yes vs no	0.51 (0.23–1.16)	2.60
pulmonary embolism[b]	yes vs no	0.99 (0.44–2.22)	0.0007
time since VTE event	1 month	0.92 (0.77–1.10)	0.86
vitamin K antagonist at the time of blood collection	yes vs no	0.63 (0.27–1.47)	1.14
vitamin K antagonist at the time of VTE recurrence	yes vs no	0.82 (0.31–2.21)	0.15
family history of VTE	yes vs no	1.30 (0.58–2.92)	0.40
lower limb varices	yes vs no	0.50 (0.15–1.68)	1.25
smoking	yes vs no	1.03 (0.44–2.42)	0.006
hs-CRP	1 log mg/l	7.96 (2.58–24.54)	13.06[f]
inherited trombophilia[c]	yes vs no	1.11 (0.46–2.68)	0.05
antiphospholipid syndrome[c]	yes vs no	0.76 (0.18–3.21)	0.14
hyperhomocysteinemia[c]	yes vs no	0.95 (0.28–3.19)	0.006
elevated factor VIII[c]	yes vs no	1.28 (0.53–3.08)	0.29
platelet count	10 g/l	0.96 (0.90–1.03)	1.22
hemoglobin	1 g/dl	0.77 (0.56–1.07)	2.41
anemia[c]	yes vs no	2.40 (0.90–6.43)	3.03
ferritin	1 log µg/l	0.54 (0.39–0.74)	14.78[f]
ID (serum ferritin <30 µg/l)	yes vs no	4.54 (2.01–10.23)	13.32[f]
T_{sat}	1%	0.97 (0.94–1.01)	2.36
T_{sat} <20%	yes vs no	2.83 (1.27–6.32)	6.43[d]
multivariate model 1			
hs-CRP	1 log mg/l	4.12 (1.33–12.79)	6.00[d]
ferritin	1 log µg/l	0.62 (0.42–0.91)	5.90[d]
T_{sat} <20%	yes vs no	0.96 (0.33–2.77)	0.006
multivariate model 2			
hs-CRP	1 log mg/l	4.52 (1.43–14.27)	6.62[d]
anemia[c]	yes vs no	1.74 (0.61–4.96)	1.08
ferritin	1 log µg/l	0.64 (0.43–0.94)	5.07[d]
T_{sat} <20%	yes vs no	0.87 (0.29–2.61)	0.06
multivariate model 3			
hs-CRP	1 log mg/l	4.39 (1.40–13.78)	6.43[d]
ID (serum ferritin <30 µg/l)	yes vs no	3.33 (1.29–8.58)	6.17[d]
T_{sat} <20%	yes vs no	1.10 (0.41–2.96)	0.03
multivariate model 4			
hs-CRP	1 log mg/l	4.77 (1.50–15.13)	7.04[e]
anemia[c]	yes vs no	1.82 (0.65–5.15)	1.29
ID (serum ferritin <30 µg/l)	yes vs no	3.17 (1.20–8.38)	5.40[d]
T_{sat} <20%	yes vs no	0.99 (0.36–2.75)	0.0005

a including those with concomitant pulmonary embolism
b including those with concomitant deep vein thrombosis
c as defined in the "Patients and Methods" section of the main text
d P <0.05; e P <0.01; f P <0.001

Abbreviations: HR, hazard ratio; others, see TABLE 1

A 2-sided P value of less than 0.05 was considered significant. Statistical analyses were conducted using the Statistica 9.1 software (Statsoft, Tulsa, Oklahoma, United States).

RESULTS

The baseline clinical characteristics of 229 patients with unprovoked VTE are shown in TABLE 1.

Prevalence of iron deficiency

ID was diagnosed in 47 subjects (21%) (TABLE 1).

Clinical and laboratory predictors of iron deficiency

In univariate logistic regression models, female sex, isolated PE and/or VTE, elevated hs-CRP levels, and low hemoglobin levels were associated with the presence of ID (TABLE 1). In multivariate logistic regression models, female sex, elevated hs-CRP levels, and low hemoglobin levels remained independent associates of ID (TABLE 1).

Iron deficiency and recurrence risk after unprovoked venous thromboembolism

The mean duration of follow-up was 13 ±6 months (range, 6–24 months). The mean time to recurrent VTE was 12 ±5 months (range, 6–23 months). The 24-month recurrence-free survival probability with 95% confidence intervals in 229 subjects with unprovoked VTE was 89.5% ±4.0%.

In univariate Cox proportional hazard regression models, the following variables were predictors of VTE recurrence during follow-up: elevated hs-CRP levels, low serum ferritin levels, T_{sat} <20%, and ID (TABLE 2). In the Kaplan–Meier curve analysis, 24-month event-free survival rates in patients with and in those without ID were 46% and 91%, respectively (P <0.001; FIGURE 1). In multivariate Cox proportional hazard regression models, the presence of ID or low serum ferritin levels remained independent prognosticators of VTE recurrence (TABLE 2).

DISCUSSION

We showed that ID is associated with an increased rate of VTE recurrence in patients with first-ever unprovoked VTE. This study is also the first to suggest a potential link of depleted iron storage with predisposition to recurrent VTE. In addition, our study provides evidence that ID, but not anemia itself, could be a novel risk factor for VTE recurrence and may help identify subjects 65 years or younger at risk of recurrent VTE.

Causes of ID in VTE patients aged 65 or younger in the current study are unclear and may involve low dietary iron intake, menorrhagia and occult bleeding. Based on this concept, one might hypothesize that, in most cases, prothrombotic state reflected by recurrent VTE is secondary to asymptomatic small blood loss. Of note, anticoagulation has not been responsible for ID in our cohort. Our data support the view that the cause of ID must be sought and dealt with, which might contribute to a reduced rate of VTE recurrence. This hypothesis warrants further investigation.

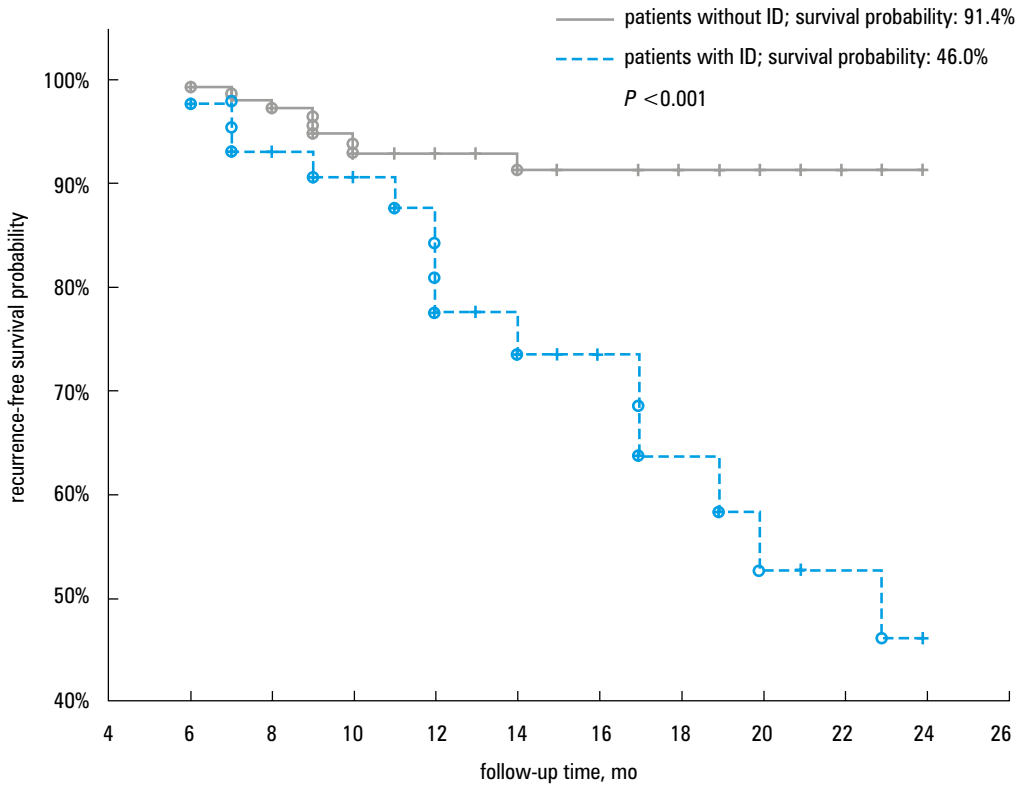

FIGURE 1 Kaplan–Meier curves showing 24-month recurrence-free survival probabilities in 229 patients with previous venous thromboembolism with or without iron deficiency (ID, defined as serum ferritin levels <30 µg/l).

Iron is a micronutrient known to be essential for hematopoietic function and oxygen transport.[15,19,20] It is well known that ID, which is present in approximately 30% of people worldwide, can lead to anemia.[15,19,20] Independently of the presence of anemia, ID itself has been demonstrated to unfavorably affect the function of various organs and systems.[15,16,19,20] Data on the association between iron metabolism and VTE are scarce. It has been reported that increased VTE risk is observed in subjects with higher hematocrit levels.[10,11]

Contrary to our expectations, we observed VTE recurrence more commonly among subjects with ID. On the other hand, in specific groups of patients, including those with inflammatory bowel disease, hereditary hemorrhagic telangiectasia, or cancer with chemotherapy-induced anemia, ID has been shown to increase the risk of VTE.[21-24] ID-related anemia has also been shown to be a risk factor for VTE in pregnant women[25] and cerebral sinovenous thrombosis in children.[26] The postulated mechanism behind those findings was reduced antioxidant defense due to ID and reduced activity of glutathion peroxidase, which corresponds to increased platelet aggregation induced both by collagen and ADP, reactive thrombocytosis, and elevated factor VIII levels.[13,21-24,27,28] In the current study, higher platelet count showed no association with ID, while elevated factor VIII levels were implicated in an increased risk of recurrent VTE. It should be stressed that thrombophilia, both inherited and acquired, also cannot explain the association between ID and VTE in our cohort.

In our study, both ID and hs-CRP levels were independent predictors of recurrent VTE in patients after an unprovoked thrombotic event. This supports the view that low-grade systemic inflammation contributes to VTE recurrence. Increased CRP levels have been shown to be associated with VTE in the general population.[29,30] CRP may be actively involved in thrombosis. For example, it has been observed that higher CRP levels are associated with the formation of dense fibrin networks less susceptible to lysis in apparently healthy subjects and those with cardiovascular disease.[31,32] Such prothrombotic fibrin clot phenotype characterized by compact fibrin architecture and its poor lysability has been reported in patients with unprovoked VTE.[33] The precise mechanisms of the links between thrombosis and ID remain to be established.

The exclusion criteria used in the present study deserve comment. Given a low VTE recurrence rate in patients with VTE provoked by transient factors,[1] we recruited patients representing a heterogeneous group of individuals with unprovoked VTE, in whom VTE may recur in 8% to 15% within the first year after discontinuation of anticoagulant therapy.[1] Moreover, subjects with the disease states that are known to be associated with anemia or ID, including heart failure, renal insufficiency, and active cancer, were also excluded to minimize confounding effects associated with additional prothrombotic mechanisms observed in those disorders.

The study has several limitations. The sample size was relatively small but was representative of unprovoked VTE patients diagnosed at the of 65 years or younger. Cases of recurrent VTE that were asymptomatic or not clinically recognized would not have been detected. Iron metabolism variables were not measured at the time of

recurrent VTE or again during follow-up. Study participants were not monitored for DVT complications, such as postthrombotic syndrome, potentially increasing the risk of VTE recurrence.[34] Next, women were overrepresented among our ID patients probably due to excessive bleeding menstruation. However, the precise analysis of menstrual blood loss was beyond the scope of this study. Finally, although patients with cancer were ineligible, we cannot exclude that occult cancer could cause ID during follow-up.

Strengths of this study include the prospective investigation of real-life consecutive patients with unprovoked VTE, who could be treated as otherwise healthy individuals free of well-known disorders associated with inflammation or iron metabolism abnormalities (or both). This study is unique in its exploration of whether iron metabolism parameters may affect the estimation of VTE recurrence risk in young and middle-aged patients at a rather low risk of recurrence.

To conclude, we demonstrated that ID is associated with an increased risk of recurrent VTE after unprovoked thrombotic episodes, which is a novel observation. It might be speculated that screening for ID in addition to other known markers may be clinically useful in identifying individuals at risk of recurrent VTE. Mechanistic studies are needed to elucidate the pathophysiology of the observed associations.

Contribution statement DPP analyzed and interpreted the data, and wrote the manuscript. EAJ participated in the study design, conducted statistical analysis, and interpreted the data. EW collected and interpreted the laboratory data. AU designed the study, recruited the patients, and reviewed the final version of the manuscript.

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ARTYKUŁ ORYGINALNY

Niedobór żelaza – nowy czynnik ryzyka nawrotu u chorych z samoistną żylną chorobą zakrzepowo-zatorową

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SŁOWA KLUCZOWE

czynnik ryzyka, niedobór żelaza, żylna choroba zakrzepowo-zatorowa (samoistna, nawrotowa)

STRESZCZENIE

WPROWADZENIE Pacjenci z samoistną żylną chorobą zakrzepowo-zatorową (ŻChZZ) narażeni są na duże ryzyko nawrotu choroby, jednak predyktory tego ryzyka pozostają w dużej mierze nieznane. Istnieją dane wskazujące na udział żelaza w patofizjologii zakrzepicy.

CELE Postanowiliśmy zbadać, czy niedobór żelaza (*iron deficiency* – ID) wpływa na ryzyko nawrotu u pacjentów po samoistnej ŻChZZ.

PACJENCI I METODY W prospektywnym badaniu kohortowym zbadano 229 kolejnych pacjentów z samoistną ŻChZZ w wieku ≤65 lat, u których w ciągu 6–12 miesięcy przed rekrutacją wystąpił pierwszy epizod ŻChZZ. Kryteria wyłączenia z badania były następujące: stężenie hemoglobiny <11 g/dl, niewydolność serca, cukrzyca, choroba nowotworowa, stężenie kreatyniny >120 μM oraz wcześniejsze lub obecne przyjmowanie preparatów żelaza i/lub czynników stymulujących erytropoezę. ID zdefiniowano jako stężenie ferrytyny w surowicy <30 μg/l. Nawroty ŻChZZ oceniano podczas 24-miesięcznej obserwacji.

WYNIKI ID stwierdzono u 47 (21%) pacjentów. W modelu regresji wielorakiej ID związany był z płcią żeńską, zwiększonym stężeniem białka C-reaktywnego (*C-reactive protein* – CRP), anemią i zmniejszonym stężeniem hemoglobiny (wszystkie p <0,05). W modelu wielowymiarowym ID (lub małe stężenie ferrytyny w surowicy) i zwiększone stężenie CRP, ale nie anemia, były predyktorami nawrotu ŻChZZ w ciągu 24 miesięcy. Hazard względny wystąpienia nawrotu wystandaryzowany na CRP i obecność anemii wynosił 3,17 dla ID (95% CI: 1,20–8,38; p = 0,02) i 0,64 dla ferrytyny (95% CI: 0,43–0,94; p = 0,02).

WNIOSKI ID może stanowić nowy czynnik ryzyka nawrotu ŻChZZ u młodych pacjentów oraz u pacjentów w średnim wieku po incydencie o niejasnej przyczynie.

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