



# The evaluation of complete blood count parameters in the patients with idiopathic versus secondary cerebral venous thrombosis

Received: 09 Dec. 2023  
Accepted: 05 Feb. 2024

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## Keywords

Cerebral Venous Thrombosis; Complete Blood Count; Red Blood Cell; Erythrocyte Indices

disease characteristics.

**Methods:** This case-control study included patients diagnosed with CVT between March 2018 and March 2021.

## Abstract

**Background:** Several laboratory markers derived from a complete blood count (CBC) have been proposed as potential indicators for assessing the risk of cerebral venous thrombosis (CVT). However, limited and conflicting evidence exists regarding this association. This study aimed to evaluate the role of CBC parameters in CVT development and their link to

**How to cite this article:** Gholamzadeh MJ, Hooshmandi E, Ghahramani Z, Fereidooni R, Rezvani A, Vasaghi-Gharamaleki M, et al. The evaluation of complete blood count parameters in the patients with idiopathic versus secondary cerebral venous thrombosis. *Curr J Neurol* 2024; 23(2): 96-105.

All participants with CVT were registered in the organized registry system at the Neurology Research Center of Shiraz University of Medical Sciences, Shiraz, Iran (CVT registry code: 9001013381). The control group consisted of age- and sex-matched individuals without systemic diseases. CBC results from the control group and the first recorded hospital CBC of the patient group were collected.

**Results:** The study included 295 patients with CVT [49 with idiopathic CVT (iCVT) and 246 with secondary CVT (sCVT)] and 341 healthy individuals. Among the CVT group, 72.54% were women. Patients with CVT had higher red cell distribution width (RDW) and lower red blood cell (RBC) count, hemoglobin (Hb) levels, and hematocrit compared to the non-CVT group. In iCVT cases, male gender, RBC count, Hb levels, and hematocrit were notably higher compared to sCVT cases. Logistic regression analysis showed that female gender, smoking, and higher hematocrit values were associated with increased probability of iCVT.

**Conclusion:** The study suggests that certain CBC parameters may serve as potential markers for assessing CVT risk and differentiating between iCVT and sCVT cases. Validation and further research are needed to explore the underlying mechanisms.

## Introduction

Cerebral venous thrombosis (CVT) is a relatively rare cerebrovascular disease that primarily affects young women and can lead to significant disability.<sup>1</sup> The exact causes of CVT are not fully understood, but multiple factors contribute to its development. These include hereditary thrombophilia, pregnancy and childbirth, postoperative conditions, intracranial and local infections, and the use of oral contraceptives.<sup>2</sup> While most CVT cases involve one or more of these risk factors, around 20% of cases are classified as idiopathic, meaning the cause is unknown.<sup>3</sup>

Previous studies have explored the relationship between blood cell parameters and thrombotic events, with a greater focus on conditions such as deep vein thrombosis (DVT)<sup>4,5</sup> and venous thromboembolism (VTE)<sup>6,7</sup> in relation to complete blood count (CBC) parameters. However, there is limited understanding of the association between CBC parameters and conditions like portal vein thrombosis (PVT),<sup>8</sup> Budd-Chiari syndrome (BCS),<sup>9</sup> and specifically, CVT.

Red blood cells (RBCs) have gained attention in recent decades concerning their role in thrombotic events, considering their impact on blood flow dynamics and interaction with the endothelium.<sup>4,10</sup> Elevated RBC levels have been linked to an increased

risk of thrombotic events.<sup>11</sup> For instance, in patients with polycythemia vera, maintaining a hematocrit level below 45% significantly reduces the incidence of major thrombosis.<sup>12-14</sup> Hematocrit levels have also been associated with venous thrombosis,<sup>13</sup> although some studies have reported conflicting findings.<sup>15,16</sup> Furthermore, higher hemoglobin (Hb) levels at admission have been correlated with an increased risk of VTE.<sup>17</sup> RBCs are believed to exert prothrombotic effects through various mechanisms, including influencing blood viscosity, adhering to vessel walls, modulating platelet reactivity, releasing microvesicles, altering membrane composition, and expressing blood group antigens.<sup>5</sup> Additionally, an elevated red cell distribution width (RDW) has been linked to a higher incidence of VTE.<sup>18,19</sup> However, the effects of RBCs on thrombotic processes are complex and can be either prothrombotic or antithrombotic, requiring further investigation to fully understand their biological role.<sup>5</sup>

Platelet adhesion to the damaged endothelium triggers a series of structural and physiological changes that initiate the coagulation cascade.<sup>20,21</sup> Larger platelet size is associated with increased activity and aggregation due to elevated thromboxane A<sub>2</sub> (TxA<sub>2</sub>) production, procoagulant activity, surface adhesion molecule expression, and enhanced aggregation capability.<sup>22</sup> However, studies investigating platelet indices such as mean platelet volume (MPV) and platelet distribution width (PDW) in CVT have generated conflicting results.<sup>23-26</sup> Bolayir and Gökçe identified higher MPV and PDW as independent risk factors for CVT.<sup>23</sup> Kamisli et al. demonstrated that patients with CVT had higher PDW values compared to the control group, while the difference in MPV between the two groups was not significant.<sup>24</sup> Another study found that PDW levels above a specific threshold were indicative of severe CVT and associated with poor functional outcomes during the early stages of admission. However, MPV and plateletcrit (PCT) did not show any effect on CVT severity and prognosis.<sup>27</sup> Some studies suggest that MPV does not significantly impact platelet function,<sup>28</sup> although an association between PDW and thrombotic events has been observed in patients with antiphospholipid syndrome.<sup>29</sup> High MPV has been linked to an increased risk of thrombosis,<sup>30</sup> ischemic stroke,<sup>31</sup> and DVT in hospitalized patients.<sup>32</sup> However, a cohort study suggests that high MPV is associated with a lower risk of VTE in patients with cancer.<sup>26</sup> A large population-based study found no relationship between MPV and

previous arterial or venous thrombosis, suggesting that the elevated MPV observed in some studies may be an acute consequence of thrombotic events rather than a causative factor.<sup>25</sup>

Furthermore, the role of inflammation in CVT has been investigated, and thrombo-inflammatory markers such as platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) have been proposed as useful indicators for the diagnosis and prognosis of CVT.<sup>33,34</sup>

Despite the potential importance of CBC parameters in the development of CVT, there is insufficient data on their role, particularly in idiopathic cases. While most studies have focused on coagulation factors found in a small portion of CVT cases, such as factor V Leiden, prothrombin gene mutation, and antithrombin deficiency,<sup>35-37</sup> there is a lack of consistent data on the relationship between CBC parameters and the pathogenesis of CVT, including whether it is based on numerical indices or their dysfunction. In this study, our objective was to evaluate CBC parameters in patients with and without known risk factors for CVT compared to healthy controls. This may offer insights into the underlying pathophysiology of CVT and contribute to a better understanding of the complex interplay of risk factors leading to the development of CVT.

## Materials and Methods

**Study design and sampling:** This study was conducted in Shiraz, Iran, in 2022. The participants consisted of patients diagnosed with CVT who were admitted to Namazi Hospital, the largest tertiary referral hospital in the southern region of Iran, between March 2018 and March 2021. All patients with CVT were included in the organized registry system developed by the Neurology Research Center of Shiraz University of Medical Sciences (CVT registry code: 9001013381). The diagnosis of CVT in all patients was confirmed through computed tomography (CT) venography and/or magnetic resonance venography (MRV). Patients with at least one of the known risk factors were classified as having secondary CVT (sCVT), while patients with no identifiable risk factors were categorized as having idiopathic CVT (iCVT).

The control group, referred to as the non-CVT group, consisted of individuals matched in terms of age and sex who did not have any known systemic diseases. These individuals visited the reference laboratory to undergo a CBC test.

Exclusion criteria for the study included individuals below 18 or above 65 years of age, a

history of ischemic stroke, pulmonary emboli, or acute myocardial infarction (MI), and the use of antiplatelet, anticoagulant, or antihyperlipidemic medications at the time of admission. In the control group, individuals with any systemic diseases were also excluded from the study.

CBC measurements were obtained from the healthy control group, as well as from the first recorded hospital CBC of the patient group, and these results were used for analysis. Blood samples for CBC analysis were collected in ethylenediamine tetraacetic acid (EDTA) tubes and analyzed using the Sysmex KX-21N Hematology Analyzer (Sysmex Corporation, Kobe, Japan). In addition to the standard CBC parameters, the following variables were also assessed: NLR, PLR, and RDW/platelet ratio (RPR). Any abnormalities observed in the CBC, such as hemoglobinopathies (sickle cell anemia, thalassemia, and iron deficiency anemia), polycythemia, thrombocytosis, and thrombocytopenia, were also recorded.

**Ethical considerations:** This study was conducted in accordance with the principles stated in the Declaration of Helsinki. The study protocol received ethical approval from the Institutional Review Board (IRB) of Shiraz University of Medical Sciences, with the approval code IR.SUMS.MED.REC.1400.478. The requirement for obtaining informed consent from participants was waived by the ethical committee due to the use of anonymous data obtained from the CVT registry, Faghihi, and Namazi hospitals.

The data were analyzed using Stata Statistical Software (Release 17, Stata Corporation, College Station, TX, USA). Independent samples t-test and Mann-Whitney U test were employed to compare the mean ranks of continuous variables, such as age and CBC parameters, among the iCVT, sCVT, and control groups. The chi-square test was used to examine gender differences among the aforementioned groups. The Lasso model was utilized for covariate selection in the regression model. Logistic regression was then performed to calculate the probability of iCVT occurrence, with age, gender, smoking, alcohol consumption, illicit drug use, family history of thrombotic events, past medical history of thrombotic events, hemoglobinopathy, and CBC parameters as covariates. Additionally, the mortality rate and different radiological findings in idiopathic cases were compared to the secondary group using the same covariates, presenting symptoms, and radiological findings. Adjusted odds ratios (AORs)

and 95% confidence interval (CI) were reported. A P-value < 0.05 was considered statistically significant.

## Results

A total of 295 patients with CVT and 341 healthy individuals were included in the study. Among the CVT cases, 16.61% (49 out of 295) were classified as iCVT. In the CVT group, 72.54% were women, while 80.89% of the sCVT cases were women and 69.39% of the iCVT cases were men. Headache was the most common symptom in both the iCVT and sCVT groups, with a prevalence of 95.92% and 91.87%, respectively. Thrombocytopenia was detected in only one individual with iCVT, compared to 10.20% of the patients with sCVT.

However, the prevalence of polycythemia, hemoglobinopathies, and thrombocytosis was similar in both groups. The most common risk factors in the CVT cases were medication use (42.37%), pregnancy-related factors (15.25%), and metabolic disorders (9.83%). Thrombosis of the superficial venous system was the most prevalent finding in both the iCVT and sCVT groups, with prevalence of 66.67% and 73.95%, respectively. The overall mortality rates were 10.20% for iCVT and 6.91% for sCVT cases. Table 1 presents an overview of the demographic, clinical, and radiological findings of the CVT cases. Tables 2 and 3 provide a summary of the qualitative and quantitative laboratory data of the patients with CVT.

**Table 1.** Demographic and clinical characteristics of idiopathic cerebral venous thrombosis (iCVT) and secondary cerebral venous thrombosis (sCVT) patients

Variable	iCVT (n = 49)	sCVT (n = 246)	Total (n = 295)
Age (year)	37.38 ± 10.20 (21-62)	37.78 ± 9.43 (18-63)	37.71 ± 9.55 (18-63)
Gender			
Women	15 (30.61)	199 (80.89)	214 (72.54)
Men	34 (69.39)	47 (19.11)	81 (27.46)
Residence			
Urban	40 (81.60)	200 (81.30)	240 (81.40)
Rural	9 (18.40)	45 (18.30)	54 (18.30)
Signs and symptoms			
Headache	47 (95.92)	226 (91.87)	273 (92.54)
Mental status disturbance	13 (26.53)	88 (35.77)	101 (34.24)
Visual symptoms	16 (32.65)	84 (34.15)	100 (33.90)
Seizure	11 (22.45)	78 (31.71)	89 (30.17)
Motor symptoms	8 (16.33)	73 (29.67)	81 (27.46)
Aphasia	3 (6.12)	44 (17.89)	47 (15.93)
Sensory symptoms	3 (6.12)	35 (14.23)	38 (12.88)
Cranial nerve palsy	5 (10.20)	32 (13.00)	37 (12.54)
Coma	1 (2.04)	11 (4.47)	12 (4.07)
Social history			
Smoking	7 (14.29)	54 (21.95)	61 (20.68)
Drug abuse	6 (12.24)	16 (6.50)	22 (7.46)
Alcohol consumption	1 (2.04)	9 (3.66)	10 (3.73)
Prior DVT/CVT events	3 (6.12)	17 (6.91)	20 (6.78)
Family history of DVT/CVT	4 (8.16)	36 (14.63)	40 (13.56)
CBC abnormality			
Hemoglobinopathy	4 (8.16)	27 (10.98)	31 (10.51)
Polycythemia	1 (1.04)	0 (2.03)	6 (2.03)
Thrombocytopenia	1 (1.04)	25 (10.20)	26 (8.81)
Thrombocytosis	1 (1.04)	0 (2.03)	6 (2.03)
Risk factors			
Medications (contraceptives, etc.)	-	-	125 (42.37)
Pregnancy-related	-	-	45 (15.25)
Metabolic disorders	-	-	29 (9.83)
Hypercoagulable state	-	-	24 (8.14)
Infection	-	-	23 (7.80)
Hematologic diseases	-	-	11 (3.73)
Other	-	-	66 (22.37)
Radiologic findings			
Thrombosis of superficial venous system	32 (66.67)	159 (73.95)	191 (72.62)
Thrombosis of deep venous systems	3 (6.25)	32 (14.88)	35 (13.31)
Thrombosis of cortical veins	2 (4.17)	32 (14.88)	34 (12.93)
Venous infarction with parenchymal hemorrhage	13 (27.08)	77 (35.81)	90 (34.22)
Mortality	5 (10.20)	17 (6.91)	22 (7.46)

Data are presented as mean ± standard deviation (SD) (minimum-maximum) or number and percent

iCVT: Idiopathic cerebral venous thrombosis; sCVT: Secondary cerebral venous thrombosis; DVT: Deep vein thrombosis; CVT: Cerebral venous thrombosis; CBC: Complete blood count

**Table 2.** Overview of quantitative laboratory data among patients with cerebral venous thrombosis (CVT)

Variable	Number of available test results (n = 295)	Mean ± SD (minimum-maximum)	Median
FBS (mg/dl)	218	108.10 ± 45.30 (53-413)	97.0
HbA1c (%)	16	6.10 ± 1.60 (5.0-11.2)	5.6
Serum iron (µg/dl)	26	89.00 ± 68.50 (26-323)	63.5
TIBC (µg/dl)	25	378.30 ± 75.30 (256-591)	379.3
Serum ferritin (ng/ml)	36	254.30 ± 503.70 (4-2400)	59.2
Prothrombin time (second)	226	20.30 ± 7.80 (11.2-67.7)	18.7
INR	223	1.80 ± 0.70 (0-5)	1.7
PTT (second)	214	40.30 ± 17.70 (20-148)	35.3
BUN (mg/dl)	223	15.80 ± 20.50 (1-252)	13.0
Serum creatinine (mg/dl)	225	1.05 ± 0.60 (0.3-8.6)	0.9
Serum sodium (mEq/l)	220	140.90 ± 6.80 (62-162)	141.0
Serum potassium (mEq/l)	220	4.15 ± 0.50 (2.5-6.7)	4.1
ALT (U/L)	183	37.30 ± 39.20 (6-360)	23.0
AST (U/l)	184	31.30 ± 32.10 (9-300)	22.0
Serum albumin (g/dl)	112	3.90 ± 0.60 (2.7-5.0)	3.9
CRP (mg/l)	181	31.46 ± 43.70 (1-150)	10.0
TSH (mIU/l)	58	2.73 ± 2.04 (0.3-12.5)	2.0
Serum TG (mg/dl)	56	145.90 ± 96.40 (41-503)	114.0
Serum cholesterol (mg/dl)	55	179.90 ± 44.40 (103-276)	174.0
HDL cholesterol (mg/dl)	55	45.00 ± 19.50 (8-139)	43.0
LDL cholesterol (mg/dl)	57	106.70 ± 38.30 (34-205)	100.0

FBS: Fasting blood sugar; HbA1c: Hemoglobin A1C; TIBC: Total iron binding capacity; INR: International normalized ratio; PTT: Partial thromboplastin time; BUN: Blood urea nitrogen; ALT: Alanine transaminase; AST: Aspartate aminotransferase; CRP: C-reactive protein; TSH: Thyroid stimulating hormone; TG: Triglyceride; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SD: Standard deviation

Table 4 demonstrates a comparison of CBC parameters between healthy individuals and the different subgroups of CVT. White blood cells

(WBCs), neutrophils, RDW, PDW, PLR, NLR, and RDW/RPR were significantly higher in patients with CVT.

**Table 3.** Overview of qualitative laboratory data among patients with cerebral venous thrombosis (CVT)

Variable	Number of available test results (n = 295)	Lower than normal range [n (%)]	Within normal range [n (%)]	Higher than normal range [n (%)]
Homocysteine	146	6 (4.0)	102 (70.0)	38 (26.0)
Variable	Number of available test results (n = 295)	Within normal range [n (%)]	Abnormal/positive test results [n (%)]	
COVID-19 PCR	36	28 (77.8)	8 (22.2)	
Protein C	120	109 (90.8)	11 (9.2)	
Protein S	116	103 (88.8)	13 (11.2)	
Anti-thrombin III	120	111 (92.5)	9 (7.5)	
Anti CD55 antibody	17	16 (94.1)	1 (5.9)	
Anti CD59 antibody	18	17 (94.4)	1 (5.6)	
Serum β-HCG	20	18 (90.0)	2 (10.0)	
Antiphospholipid IgM	116	112 (96.6)	4 (3.4)	
Antiphospholipid IgG	121	119 (98.3)	2 (1.7)	
Lupus anticoagulant IgM	51	44 (86.3)	7 (13.7)	
Lupus anticoagulant IgG	90	63 (70.0)	27 (30.0)	
Anti-nuclear antibody	187	177 (94.7)	10 (5.3)	
Anti-dsDNA antibody	176	165 (93.8)	11 (6.3)	
Anti β2 glycoprotein IgM	110	102 (92.7)	8 (7.3)	
Anti β2 glycoprotein IgG	116	106 (91.4)	10 (8.6)	
Anticardiolipin IgM	99	97 (98.0)	2 (2.0)	
Anticardiolipin IgG	126	122 (96.8)	5 (3.2)	
p-ANCA	148	144 (97.3)	4 (2.7)	
c-ANCA	137	136 (99.3)	1 (0.7)	
Jak2 mutation	77	2 (2.6)	77 (97.4)	

COVID-19: Coronavirus disease 2019; PCR: Polymerase chain reaction; HCG: Human chorionic gonadotropin; IgM: Immunoglobulin M; IgG: Immunoglobulin G; p-ANCA: Perinuclear anti-neutrophil cytoplasmic antibody; c-ANCA: Cytoplasmic anti-neutrophil cytoplasmic antibody; dsDNA: Double-stranded deoxyribonucleic acid

**Table 4.** Overview of complete blood count (CBC) parameters among different subgroups of cerebral venous thrombosis (CVT) and non-CVT

Variable	Total CVT (n = 295)	Non-CVT group (n = 341)	P	iCVT (n = 49)	sCVT (n = 246)	P <sup>#</sup>
Age (year)	37.72 ± 9.55 (18-63)	38.79 ± 10.74 (18-65)	0.190	37.38 ± 10.20 (21-62)	37.78 ± 9.43 (18-63)	0.790
Gender						
Men	81 (27.46)	97 (28.45)	0.782 <sup>s</sup>	34 (69.39)	47 (19.11)	< 0.001 <sup>s</sup>
Women	214 (72.54)	244 (71.55)		15 (30.61)	199 (80.89)	
WBC (×10 <sup>3</sup> /μl)	10.56 ± 4.05 (1.20-26.70)	6.61 ± 1.28 (4.50-10.13)	< 0.001 <sup>*</sup>	10.30 ± 3.59 (4.80-18.30)	10.61 ± 4.15 (1.20-26.70)	0.623 <sup>*</sup>
Lymphocytes (×10 <sup>3</sup> /μl)	1.94 ± 1.17 (0.20-9.51)	2.43 ± 0.57 (1.17-4.30)	< 0.001 <sup>*</sup>	2.38 ± 1.39 (0.68-9.26)	1.86 ± 1.11 (0.20-9.51)	0.002 <sup>*</sup>
Neutrophils (×10 <sup>3</sup> /μl)	8.13 ± 3.79 (0.78-23.04)	3.53 ± 0.84 (1.96-6.66)	< 0.001 <sup>*</sup>	7.52 ± 3.41 (2.93-15.14)	8.25 ± 3.86 (0.78-23.04)	0.276
RBC (×10 <sup>6</sup> /μl)	4.71 ± 0.69 (2.83-7.87)	4.96 ± 0.37 (4.00-5.90)	< 0.001	5.17 ± 0.48 (4.19-6.23)	4.62 ± 0.70 (2.83-7.87)	< 0.001
Hemoglobin (g/dl)	13.23 ± 2.23 (6.80-19.10)	14.26 ± 1.05 (12.00-16.80)	< 0.001 <sup>*</sup>	14.90 ± 1.57 (12.20-18.20)	12.88 ± 2.19 (6.80-19.10)	< 0.001
Hematocrit (%)	40.22 ± 6.10 (13.10-64.20)	42.83 ± 2.70 (36.10-54.10)	< 0.001	44.57 ± 3.91 (36.30-56.00)	39.33 ± 6.10 (13.10-64.20)	< 0.001 <sup>*</sup>
MCV (fl)	85.91 ± 7.65 (56.50-118.30)	86.11 ± 3.20 (80.00-95.80)	0.326 <sup>*</sup>	86.43 ± 6.14 (71.50-103.80)	85.80 ± 7.93 (56.50-118.30)	0.953 <sup>*</sup>
MCH (pg)	28.22 ± 3.47 (15.20-39.90)	28.67 ± 1.24 (25.30-32.00)	0.974 <sup>*</sup>	28.87 ± 2.62 (23.60-35.50)	28.09 ± 3.62 (15.20-39.90)	0.349 <sup>*</sup>
RDW (%)	14.34 ± 2.21 (11.60-22.70)	13.13 ± 0.64 (11.20-14.50)	< 0.001 <sup>*</sup>	13.43 ± 1.29 (11.80-18.50)	14.56 ± 2.32 (11.60-22.70)	0.001 <sup>*</sup>
Platelet (×10 <sup>3</sup> /μl)	252.53 ± 109.83 (35.00-1124.00)	255.09 ± 51.38 (161.00-441.00)	0.060 <sup>*</sup>	254.65 ± 83.00 (149.00-566.00)	252.10 ± 114.69 (35.00-1124.00)	0.885 <sup>*</sup>
MPV (fl)	9.83 ± 1.18 (7.60-15.30)	9.61 ± 0.91 (7.70-12.60)	0.066 <sup>*</sup>	9.86 ± 1.09 (7.60-13.20)	9.82 ± 1.21 (7.60-15.30)	0.617 <sup>*</sup>
PDW (fl)	14.78 ± 8.79 (8.80-49.80)	11.00 ± 1.88 (7.70-17.50)	< 0.001 <sup>*</sup>	15.22 ± 9.31 (8.90-47.10)	14.69 ± 8.69 (8.80-49.80)	0.580 <sup>*</sup>
P-LCR (%)	22.22 ± 7.46 (7.80-45.60)	22.49 ± 6.56 (9.00-43.60)	0.655	22.43 ± 7.91 (7.80-38.80)	22.18 ± 7.38 (8.50-45.60)	0.841
PCT (%)	0.24 ± 0.09 (0.03-1.01)	0.24 ± 0.04 (0.14-0.39)	0.473 <sup>*</sup>	0.24 ± 0.07 (0.15-0.51)	0.25 ± 0.10 (0.03-1.01)	0.986 <sup>*</sup>
PLR	171.56 ± 143.44 (16.51-1343.87)	109.31 ± 29.34 (54.68-237.46)	< 0.001 <sup>*</sup>	127.81 ± 59.26 (30.88-273.53)	180.10 ± 153.26 (16.51-1343.87)	0.043 <sup>*</sup>
NLR	5.99 ± 6.62 (0.68-86.00)	1.50 ± 0.42 (0.81-2.94)	< 0.001 <sup>*</sup>	4.00 ± 2.93 (0.94-13.13)	6.38 ± 7.06 (0.68-86.00)	0.005 <sup>*</sup>
RPR	0.07 ± 0.05 (0.01-0.39)	0.05 ± 0.01 (0.03-0.08)	< 0.001 <sup>*</sup>	0.05 ± 0.01 (0.02-0.01)	0.07 ± 0.05 (0.01-0.39)	0.226 <sup>*</sup>

Data are presented as mean ± standard deviation (SD) (minimum-maximum) or number and percent

<sup>#</sup>P-value is calculated from two independent samples t-test; \*P-value is calculated from Mann-Whitney U test because of non-normal distribution; <sup>s</sup>P-value is calculated from chi square test in crosstabs

iCVT: Idiopathic cerebral venous thrombosis; sCVT: Secondary cerebral venous thrombosis; CVT: Cerebral venous thrombosis; WBC: White blood cells; RBC: Red blood cells; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; RDW: Red cell distribution width; MPV: Mean platelet volume; PDW: Platelet distribution width; P-LCR: Platelet-large cell ratio; PCT: Plateletcrit; PLR: Platelet/lymphocyte ratio; NLR: Neutrophil/lymphocyte ratio; RPR: Red cell distribution width/platelet ratio

On the other hand, lymphocytes, RBCs, Hb, and hematocrit were significantly lower in patients with CVT compared to the non-CVT group. In terms of gender-specific differences within the CVT subgroups, male gender, lymphocytes, RBC, Hb, and hematocrit were notably higher in iCVT

cases compared to sCVT cases. Conversely, female gender, RDW, PLR, and NLR were lower in patients with iCVT.

In the logistic regression model, after adjusting for the covariates selected in the Lasso model, female gender and smoking were associated with

a lower probability of developing iCVT (AOR = 0.04, 95% CI = 0.01-0.18, P < 0.001, and AOR = 0.26, 95% CI = 0.07-0.96, P = 0.043, respectively). Among the CBC parameters, only hematocrit values above the normal reference range had a significant association with a higher likelihood of iCVT (AOR = 15.98, 95% CI = 1.05-242.44, P = 0.046). Table 5 presents the logistic regression model for the occurrence of iCVT compared to sCVT.

Table 6, available in the supplementary data, presents the association of iCVT with mortality and radiological findings compared to sCVT. There were no significant differences in terms of mortality rates and the occurrence of parenchymal hemorrhage, cortical, superficial, or deep venous system thrombosis between iCVT and sCVT cases.

**Discussion**

Our findings demonstrated significant variations in CBC parameters between patients with CVT and healthy individuals, as well as between iCVT and sCVT cases. Specifically, elevated hematocrit values beyond the normal range were significantly associated with a higher likelihood of iCVT.

The total WBC and neutrophil counts were higher in the CVT group, while the lymphocyte

count was lower. Venous wall injury can trigger acute systemic inflammation, leading to an increase in WBCs and neutrophils.<sup>38</sup> Our data align with this evidence, showing elevated WBC and neutrophil counts and reduced lymphocyte count in patients with CVT. Notably, lymphocyte count was significantly higher in the iCVT group compared to the sCVT group.

Our study revealed that PLR and NLR were significantly elevated in patients with CVT. However, there is conflicting evidence regarding the association of these ratios with CVT. While some studies have reported no overall increased risk of VTE or CVT with PLR,<sup>39</sup> NLR,<sup>40</sup> and MPV<sup>24</sup> values, others have identified them as independent predictors and diagnostic factors of CVT.<sup>23,33,41</sup> In particular, PLR has been associated with disease severity, recurrence, and poor outcomes.<sup>34,42,43</sup> High PLR values have been linked to an increased risk of sCVT.<sup>39</sup> A study by Tekesin and Tunc suggested the use of NLR and PLR as cost-effective and widely available parameters for predicting CVT in suspected patients.<sup>42</sup> However, our results contradict the findings of Kamisli et al., who proposed a correlation between MPV and PDW with brain parenchymal lesions observed in imaging.<sup>24</sup>

**Table 5.** Association of different parameters with idiopathic cerebral venous thrombosis (iCVT)

Variable		AOR** (95% CI)	P
Age (year)	Under 30	Ref.	-
	30-44	1.99 (0.63-6.29)	0.239
	45 or older	2.91 (0.61-13.96)	0.181
Gender	Men	Ref.	-
	Women	0.04 (0.01-0.18)	< 0.001*
Smoking		0.26 (0.07-0.96)	0.043*
Illicit drug use		0.44 (0.07-2.63)	0.367
Family history of DVT or CVT		0.20 (0.03-1.26)	0.087
Hemoglobin	Below reference range or normal	Ref.	-
	Higher than reference range	2.81 (0.66-11.99)	0.163
Hematocrit	Below reference range or normal	Ref.	-
	Higher than reference range	15.98 (1.05-242.44)	0.046*
Lymphocyte count	Below reference range	Ref.	-
	Normal	6.00 (0.55-65.56)	0.142
	Higher than reference range	5.42 (0.34-86.13)	0.231
PCT	Below reference range	Ref.	-
	Normal	0.55 (0.13-2.30)	0.412
PLR	Higher than reference range	1.51 (0.55-4.20)	0.425
	Below reference range	Ref.	-
	Normal	0.16 (0.01-3.31)	0.236
	Higher than reference range	0.08 (0.00-2.02)	0.125

\*Statistically significant; \*\*Adjusted for age, gender, smoking, alcohol consumption, illicit drug consumption, family history of thrombotic events, past medical history of thrombotic events, including hemoglobinopathy and complete blood count (CBC) parameters

AOR: Adjusted odds ratio; DVT: Deep vein thrombosis; CVT: Cerebral venous thrombosis; PCT: Plateletcrit; PLR: Platelet/lymphocyte ratio; CI: Confidence interval

**Table 6.** Association of idiopathic cerebral venous thrombosis (iCVT) with mortality and radiologic findings

Outcome variable	AOR* for iCVT as a predictor for the outcome variable (95% CI)	P
Mortality	1.63 (0.23-11.30)	0.622
Parenchymal hemorrhage	2.03 (0.75-5.45)	0.163
Cortical vein thrombosis	0.22 (0.03-1.56)	0.128
Superficial vein thrombosis	0.61 (0.20-1.88)	0.386
DVT	0.31 (0.05-2.05)	0.226

\*Adjusted for age, gender, smoking, family history of thrombotic events, illicit drug use, past medical history of thrombotic events, hemoglobinopathy, and complete blood count (CBC) parameters

AOR: Adjusted odds ratio; DVT: Deep vein thrombosis; iCVT: Idiopathic cerebral venous thrombosis; CI: Confidence interval

RBC indices may also play a role in VTE and CVT. Previous studies have linked VTE to elevated hematocrit levels.<sup>17,44</sup> In our study, we found that higher hematocrit levels were associated with iCVT cases, suggesting that hypercoagulable states like primary polycythemia increase the risk of CVT.<sup>45</sup> Increasing hematocrit levels, whether through increased erythropoiesis or packed cell transfusions, has been shown to increase the risk of VTE in patients with anemia and polycythemia vera, respectively.<sup>46,47</sup> Conversely, maintaining a hematocrit level below 45% has been associated with a fourfold decrease in thrombosis risk.<sup>12</sup>

Interestingly, we observed lower values of RBC count, Hb concentration, and hematocrit, as well as higher levels of RDW, in patients with CVT compared to healthy individuals. These differences were also present when comparing the sCVT group to idiopathic cases. The controversy surrounding these findings may stem from the fact that these RBC indices themselves may not be accurate indicators of thrombosis susceptibility. In the case of sCVT, patients often have underlying diseases that can affect RBC production due to the presence of an inflammatory state, similar to anemia of chronic disease. However, high RDW has been identified as an independent risk factor for VTE incidence.<sup>18,48</sup> Individuals with RDW values above the 90<sup>th</sup> percentile have an almost fourfold increased risk of CVT compared to those with RDW values equal to or below the 90<sup>th</sup> percentile.<sup>49</sup> One possible explanation for this finding is that greater variation in RBC volumes is associated with decreased RBC deformability, which in turn increases the risk of thrombotic events.

A study by Patel et al. found that higher RDW values, specifically greater than 14.0%, were associated with reduced RBC deformability.<sup>19</sup> Additionally, Ananthaseshan et al. reported that RDW might impact thromboembolic pathways through its interaction with vascular walls. RDW was associated with the formation of atherosclerotic plaques, increased inflammatory

response in atherosclerotic lesions, higher interactions between blood cells and vascular walls, and changes in blood flow patterns, all of which can contribute to the development of atherosclerosis.<sup>14</sup> These findings suggest that the role of RBC deformability may extend beyond a mere hypothesis and should be thoroughly investigated in relation to other thrombotic events.

Moreover, our findings indicate that being woman and smoking are associated with a lower likelihood of developing iCVT. CVT predominantly affects younger individuals, particularly women of reproductive age.<sup>50,51</sup> In our study, the male-to-female ratio in the CVT group was 1:2.64, and in the sCVT group, it was 1:4.23. However, in the iCVT group, the ratio was 2.27:1. Other studies have reported a higher prevalence of CVT in women, ranging from 3.7 to 5.3 times more female patients than male patients.<sup>52,53</sup> This difference may be attributed to gender-specific risk factors such as pregnancy, the postpartum period, and the use of oral contraceptives.<sup>54,55</sup> Smoking has been suggested as a potential risk factor for cerebrovascular disease, and it is known to be one of the leading causes of cerebral infarction among smokers.<sup>56</sup> There have been cases where smoking was identified as the sole risk factor and a possible cause of secondary polycythemia in individuals with CVT.<sup>57</sup> Nevertheless, the evidence regarding the association between smoking and the risk of CVT development is conflicting, as some studies have reported no significant link.<sup>58-60</sup>

**Limitations:** One of the strengths of this study is its large sample size compared to previous studies, which enhances the reliability and credibility of our results. Additionally, this is the first study to comprehensively evaluate CVT cases without previously identified risk factors. However, there are limitations to consider. This study was observational in nature, which means it cannot establish a cause-and-effect relationship between CBC parameters and the occurrence of CVT. Furthermore, pre-admission CBC parameters for



the CVT group were not available, and these values could have provided valuable information about whether platelet indices changed after the onset of CVT or if they remained consistent, thus serving as reliable predictive factors.

### Conclusion

Significant differences exist in CBC parameters between CVT cases and healthy individuals. While these parameters vary between idiopathic and secondary groups, higher hematocrit levels were specifically associated with iCVT. Furthermore, iCVT did not show any association with clinical data, radiologic findings, or prognostic outcomes. Additional studies are needed to investigate the

potential role of novel blood cell characteristics, including RBC deformability, in CVT.

### Conflict of Interests

The authors declare no conflict of interest in this study.

### Acknowledgments

We would like to thank Daneshbod Pathology Laboratory and Namazi Hospital in Shiraz which generously provided us with the required clinical, laboratory, and radiological data.

This study was financially supported by the Office of Vice Chancellor for Research at Shiraz University of Medical Sciences (Grant No: 24455).

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