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RESEARCH ARTICLE

Red blood cell distribution width is a useful biomarker to predict bleeding and thrombosis risks in patients with immune thrombocytopenic purpura

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Abstract

Bleeding and thrombosis are common complications during immune thrombocytopenic purpura (ITP) treatment. There is a strong need to predict bleeding and thrombosis risks before ITP treatment to optimize therapy and appropriately manage these complications. We performed a retrospective cohort study of 120 patients with primary ITP to identify a biomarker to predict bleeding and thrombosis. We compared blood test results at diagnosis between patients with and without bleeding or thrombosis episodes. The standard deviation of red blood cell distribution width (RDW-SD) differed significantly between those with and without bleeding and between those with and without thrombosis, leading us to identify it as a variable representative of risk. RDW-SD was significantly associated with patient age and with histories of several vascular diseases. Multivariate regression analyses showed that RDW integrated several variables associated with vascular risks. RDW-SD was significantly associated with difficulty with corticosteroid discontinuation (hazard ratio [HR], 2.22, $p = 0.01$), incidence of bleeding (HR, 2.75, $p < 0.01$), incidence of thrombosis (HR, 2.67, $p < 0.01$) and incidence of infection (HR, 1.78, $p = 0.04$). The RDW-SD value at the time of ITP diagnosis is a useful biomarker to predict the risks of bleeding, thrombosis, and other complications.

KEYWORDS
biomarker, bleeding, immune thrombocytopenic purpura, red blood cell distribution width, thrombosis

1 | INTRODUCTION

Immune thrombocytopenic purpura (ITP) is an acquired autoimmune disease characterized by thrombocytopenia that is mediated through the production of antiplatelet autoantibodies [1–3]. Bleeding, such as nasal and gastrointestinal hemorrhage, is the most common complication right before and after the initiation of corticosteroid therapy [4, 5]. Because of the high titer of antibodies against platelets, transfusion has little effect, and the patient often experiences difficulty with hemostasis [6]. The Japanese ITP guidelines recommend corticosteroid pulse therapy and intravenous immunoglobulin therapy as the treatment strategy for adult ITP patients with acute bleeding [7]. The

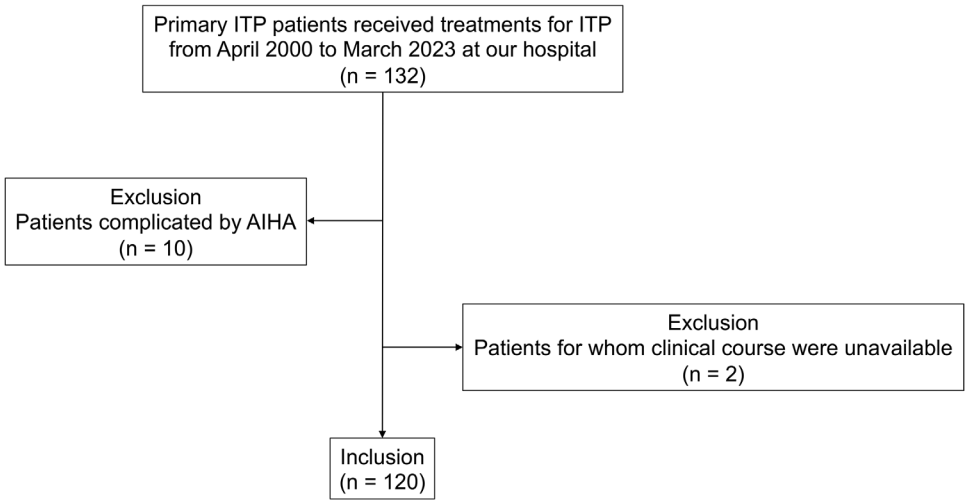

FIGURE 1 CONSORT diagram showing patient selection. AIHA, Autoimmune hemolytic anemia; ITP, immune thrombocytopenic purpura.

risk of both venous and arterial thrombosis is 3–4 times higher in ITP patients than in healthy people [8, 9], and thrombosis sometimes becomes a serious problem after platelet recovery through treatments for ITP—especially treatment with thrombopoietin-receptor agonist (TPO-RA) [10–12]. Therefore, there is a strong need to predict risks of bleeding and thrombosis in order to optimize the ITP treatment [13] and to appropriately manage bleeding and thrombosis [14, 15].

In this study, we sought to identify a reliable biomarker that can predict risks of bleeding and thrombosis before the initiation of the first-line corticosteroid therapy. We focused on laboratory data at diagnosis in relation to the risks of bleeding and thrombosis during the treatment course, and we identified red blood cell distribution width (RDW) as a novel predictive biomarker. We believe that its clinical use will improve the ITP management.

2 | METHODS

2.1 | Patients

This retrospective study included consecutive adult patients who received the corticosteroid therapy for primary ITP from April 2000 to March 2023 at Shinko Hospital. Patients with the complication of autoimmune hemolytic anemia and those for whom the clinical course was unavailable were excluded (Figure 1). The diagnosis and treatment strategy were based on the Japanese ITP guideline [7]. This study was approved by the Institutional Review Board and Ethics Committee of Shinko Hospital.

2.2 | Endpoints and definitions

The primary endpoints were the incidences of bleeding and thrombosis during the treatment for ITP. The secondary endpoints were the rate of resistance to the first-line corticosteroid therapy, defined as an increase in platelet count to no more than 30×10^9/L without transfusion within 3 weeks after the initiation of the corticosteroid therapy; the rate of non-achievement of complete response (CR), with CR defined as any platelet count of at least 100×10^9/L without transfusion; [1, 14] the rate of difficulty with corticosteroid discontinuation, defined as the need to continue oral corticosteroids for more than 6 months after the initiation of the corticosteroid therapy; the incidence of venous and arterial thromboses caused by the treatment for ITP; and the incidence of infection due to the treatment for ITP, defined as infectious episodes requiring antibiotics or antiviral drugs during treatment course. All diagnoses of ITP were in accordance with the guideline published in 2009 by Rodegheiro [1]. The standard deviation of RDW (RDW-SD) in peripheral blood was measured by using a Sysmex XN-10-B3 Hematology Analyzer (Sysmex, Japan). Measurement of platelet-associated IgG by using an enzyme-linked immunosorbent assay was outsourced to an external laboratory (SRL, Tokyo, Japan; normal, ≤ 46 ng/10^7 cells).

2.3 | Statistical analysis

Continuous variables were summarized by using medians and ranges, and categorical variables were summarized as counts and percentages. For comparisons between groups, patient and disease characteristics were compared by using Student's *t*-test or ANOVA for continuous variables and Fisher's exact test for categorical variables. Comprehensive correlation between individual laboratory markers and the parameters was evaluated by using Pearson's correlation coefficient. Multiple regression analysis was used to assess the relationships between RDW-SD and two variables (patient age and number of comorbidities with vascular risks) at the time of ITP diagnosis. Accuracy of prediction with an approximate formula obtained from multiple regression analysis was assessed with Fisher's exact test. Statistical significance was set at $p < 0.05$. All statistical analyses were performed with EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) or STATA version 16.0 (Stata Corp, TX) [16].

TABLE 1 Patient characteristics.

Total, *n*	120
Age (years), median (range)	73 (35–97)
Sex (male/female), *n* (%)	56 (46.7)/64 (53.3)
Bleeding episode, *n* (%)	33 (27.5)
Nasal hemorrhage	22 (18.3%)
Gastrointestinal hemorrhage	12 (10.0%)
Intracranial hemorrhage	2 (1.7%)
Thrombosis episode, *n* (%)	21 (17.5)
Venous thrombosis	14 (11.7%)
Arterial thrombosis	10 (8.3%)
Primary ITP, *n* (%)	120 (100)
Secondary ITP, *n* (%)	0 (0)
AIHA (Evans syndrome), *n* (%)	0 (0)
History of hypertension, *n* (%)	40 (33.3)
History of hyperlipidaemia, *n* (%)	35 (29.2)
History of diabetes, *n* (%)	17 (14.2)
History of CKD, *n* (%)	16 (13.3)
History of ischemic heart disease, *n* (%)	10 (8.3)
History of malignant tumor, *n* (%)	11 (9.2)
History of osteoporosis, *n* (%)	22 (18.6)
Current smoker, *n* (%)	18 (15.0)
Past smoker, *n* (%)	45 (37.5)
Type and initial dose of corticosteroid as first-line therapy, *n* (%)	
PSL 1 mg/kg/day	93 (77.5%)
PSL 0.5 mg/kg/day	27 (22.5%)
Additional therapies as second- or higher-line therapy, *n* (%)	
TPO-RA	45 (90.0%)
Rituximab	6 (12.0%)
Splenectomy	3 (6.0%)
Helicobacter pylori eradication, *n* (%)	31 (25.8)
Intravenous γ-globulin, *n* (%)	10 (8.3)

Abbreviations: AIHA, Autoimmune hemolytic anemia; CKD, chronic kidney disease; ITP, immune thrombocytopenic purpura; PAIgG, platelet-associated IgG; PSL, prednisolone; TPO-RA, thrombopoietin-receptor agonist.

3 | RESULTS

3.1 | Patient characteristics

This study included 120 patients with primary ITP (median age, 73 years; Table 1). During the treatment for ITP, bleeding was observed in 33 (27.5%) patients and thrombosis in 21 (17.5%). At diagnosis with ITP, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease (CKD), ischemic heart disease, malignant tumor, and osteoporosis were complicated in 40 (33.3%), 35 (29.2%), 17 (14.2%), 16 (13.3%), 10 (8.3%), 11 (9.2%), and 22 (18.6%) cases, respectively. Prednisolone was used as a first-line therapy in all of the patients; second-line therapies of TPO-RA (eltrombopag or romiplostim), rituximab or splenectomy were given to 50 patients. Median follow-up time after diagnosis of ITP was 5.7 years.

3.2 | Extraction of a biomarker to predict the risks of bleeding and thrombosis

Of 33 patients with a bleeding episode, bleeding was observed within 1 month after diagnosis in 32 (97.0%) cases. Of 21 patients with a thrombosis episode, thrombosis was observed during the treatment with corticosteroid in 6 (28.6%), TPO-RA in 19 (90.5%), and rituximab in 1 (4.8%). Of 120 total patients, three underwent splenectomy, and venous thrombosis was observed within 1 year after splenectomy in two of the three (66.7%). Classification of thrombosis (venous or arterial) had no relevance to the treatment for ITP.

To identify a biomarker to predict the risks of bleeding and thrombosis during the treatment for ITP, we first categorized the patients into those with a bleeding episode during the course of treatment [bleeding (+) cohort] and those without [bleeding (−) cohort], and into patients with a thrombosis episode [thrombosis (+) cohort] and those without [thrombosis (−) cohort]. Then, we compared the results of several blood tests at the time of diagnosis with ITP. The number of the patients with both bleeding and thrombosis episodes, with bleeding episodes without thrombosis episodes, without bleeding episodes with thrombosis episodes, and without both bleeding and thrombosis episodes, were 11, 22, 10, and 77, respectively. Of 11 patients with both bleeding and thrombosis episodes, 10 had thrombosis episodes after bleeding episodes and 1 had a bleeding episode after a thrombosis episode. Prior bleeding or thrombosis episodes might affect the risks of bleeding or thrombosis, so we excluded 10 patients with thrombosis episodes after bleeding episodes from the thrombosis (+) cohort, and 1 patient with a bleeding episode after a thrombosis episode from the bleeding (+) cohort. RDW-SD and RDW-CV differed significantly between the (+) and (−) groups, and this difference held for both the bleeding cohort and the thrombosis cohort (Table 2). Evaluation methods are different, but both RDW-SD and RDW-CV quantify variation of red blood cell size. RDW-SD and RDW-CV were strongly correlated (Pearson correlation coefficient [PCC], 0.878, $P < 0.01$, Figure S1). We selected RDW-SD as representative of RDW in subsequent analyses. Oral medication rates of antiplatelet and anticoagulant agents at diagnosis with ITP were comparable between the cohorts with and without bleeding/thrombosis. The type of TPO-RA used (eltrombopag or romiplostim) was also comparable among the four cohorts.

3.3 | Relationship between multiple vascular risks and red blood cell distribution width at diagnosis with standard deviation of immune thrombocytopenic purpura

We tested the relationships between multiple vascular risks and RDW-SD values at the time of diagnosis with ITP (Table 3). Patient age

TABLE 2 Comparison of blood test results at diagnosis between cohorts with and without a bleeding or thrombosis episode in the course of treatment.

	Bleeding (+) ($n = 32$)	Bleeding (−) ($n = 87$)	p	Thrombosis (+) ($n = 11$)	Thrombosis (−) ($n = 99$)	p
Blood test at diagnosis, median (range)						
WBC ($\times 10^9$/L)	6.0 (2.0–11.2)	5.8 (2.1–10.2)	0.89	5.5 (2.2–10.5)	6.1 (2.0–11.2)	0.81
Neut ($\times 10^9$/L)	4.4 (1.0–7.2)	4.2 (0.9–7.7)	0.90	4.0 (0.9–6.9)	4.4 (1.0–7.7)	0.79
Lymph ($\times 10^9$/L)	2.1 (0.8–5.5)	2.2 (0.9–5.4)	0.91	2.0 (0.9–5.2)	2.2 (0.8–5.5)	0.93
Mono ($\times 10^9$/L)	0.42 (0.18–0.80)	0.39 (0.16–0.85)	0.89	0.46 (0.21–0.85)	0.39 (0.16–0.80)	0.67
Eosino ($\times 10^9$/L)	0.08 (0.02–0.12)	0.07 (0.02–0.14)	0.91	0.08 (0.03–0.12)	0.08 (0.02–0.14)	0.95
Baso ($\times 10^9$/L)	0.07 (0.02–0.13)	0.08 (0.03–0.15)	0.95	0.08 (0.03–0.14)	0.08 (0.02–0.15)	0.97
Hb (g/dL)	13.9 (8.9–18.0)	14.4 (9.1–18.1)	0.63	14.0 (9.2–17.5)	14.3 (8.9–18.1)	0.59
MCV (fL)	88.5 (72.3–103.7)	84.8 (74.5–100.9)	0.33	88.2 (74.5–103.7)	85.2 (72.3–100.9)	0.57
MCH (pg)	30.0 (26.5–34.3)	30.3 (26.9–34.0)	0.89	30.3 (27.3–34.0)	30.1 (26.5–34.3)	0.89
MCHC (%)	33.3 (30.5–37.5)	32.9 (30.8–36.3)	0.69	33.6 (30.8–37.5)	33.0 (30.3–37.2)	0.56
RDW-SD (fL)	52.5 (42.5–72.5)	45.5 (36.5–57.9)	0.01	53.7 (45.0–72.5)	44.9 (36.5–62.3)	0.02
RDW-CV (%)	17.2 (13.3–20.8)	14.6 (10.8–18.4)	0.01	17.0 (13.2–20.8)	14.6 (10.8–18.8)	0.02
Reti (‰)	5.2 (2.2–15.0)	4.9 (1.9–18.2)	0.81	5.4 (2.2–16.2)	4.9 (1.9–18.2)	0.44
Plt ($\times 10^9$/L)	8 (1–27)	10 (1–27)	0.50	8 (2–20)	9 (1–27)	0.78
MPV (fL)	11.5 (9.0–12.7)	11.8 (9.5–13.2)	0.89	11.7 (9.8–13.2)	11.3 (9.0–13.0)	0.67
PDW (g/dL)	14.6 (11.3–18.9)	14.0 (10.7–18.1)	0.78	14.9 (11.3–18.9)	14.0 (11.0–18.1)	0.81
Pct (%)	0.059 (0–0.10)	0.049 (0–0.15)	0.89	0.063 (0–0.15)	0.047 (0–0.10)	0.59
PAIgG (ng/10^7 cells)	445 (54–9890)	467 (45–12,400)	0.75	498 (54–12400)	444 (45–9890)	0.56
AST (IU/L)	27 (15–81)	25 (15–67)	0.81	27 (15–81)	24 (15–72)	0.89
ALT (IU/L)	30 (13–90)	26 (10–88)	0.81	28 (13–88)	27 (10–90)	0.90
LDH (IU/L)	197 (108–273)	183 (99–247)	0.33	199 (111–273)	181 (99–247)	0.24
ALP (IU/L)	180 (80–275)	188 (85–282)	0.75	178 (82–282)	189 (80–265)	0.72
γ-GTP (IU/L)	28 (12–89)	33 (13–105)	0.67	32 (14–105)	29 (12–89)	0.72
Cre (mg/dL)	0.87 (0.52–1.45)	0.75 (0.45–1.15)	0.26	0.89 (0.60–1.45)	0.72 (0.45–1.32)	0.31
UA (mg/dL)	5.2 (2.0–10.5)	4.6 (1.5–8.8)	0.56	5.4 (2.0–10.5)	4.5 (1.5–8.8)	0.39
BUN (mg/dL)	18 (8–38)	14 (6–35)	0.78	17 (6–38)	16 (8–35)	0.75
TP (g/dL)	7.2 (6.0–9.5)	7.2 (6.8–9.2)	0.91	7.1 (6.0–9.2)	7.3 (6.3–9.5)	0.91
Alb (g/dL)	4.2 (1.9–5.1)	4.5 (2.9–5.2)	0.69	4.1 (1.9–5.2)	4.5 (2.3–5.1)	0.67
Na (mEq/L)	144 (130–152)	140 (128–149)	0.78	141 (128–152)	143 (130–149)	0.88
K (mEq/L)	4.1 (3.3–5.0)	4.1 (3.0–5.2)	0.91	4.2 (3.3–5.2)	4.1 (3.0–5.0)	0.75
Cl (mEq/L)	105 (95–112)	102 (89–108)	0.78	106 (89–112)	102 (95–108)	0.89
CRP (mg/dL)	0.2 (0.1–2.4)	0.2 (0.1–1.8)	0.67	0.2 (0.1–2.4)	0.2 (0.1–1.8)	0.69

Abbreviations: Alb, Albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Baso, basophil; BUN, blood urea nitrogen; Cl, chlorine; Cre, creatinine; CRP, C-reactive protein.; Eosino, eosinophil; Hb, hemoglobin; K, potassium; LDH, lactate dehydrogenase; Lymph, lymphocyte; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; Mono, monocyte; MPV, mean platelet volume; Na, sodium; Neut, neutrophil; PAIgG, platelet-associated IgG; Pct, plateletcrit; PDW, platelet distribution width; Plt, platelet; RDW-CV, red blood cell distribution width-coefficient of variation; RDW-SD, standard deviation of red blood cell distribution width; Reti, reticulocytes; TP, total protein; UA, uric acid;WBC, white blood cell; γ-GTP, gamma-glutamyl transpeptidase.

and RDW-SD were strongly correlated (PCC, 0.79, $p = 0.02$). RDW-SD values were also significantly associated with histories of cardiovascular disease, hypertension, hyperlipidaemia, diabetes mellitus, CKD, and malignant tumor. In the multivariate analyses (Table 4), bleeding risks were significantly related to RDW-SD value and patient age. On the basis of the multivariate regression analyses, RDW-SD value at the time of ITP diagnosis (in femtoliters, fL) was explained by patient age and number of comorbidities with vascular risks by using the following formula: Estimated value of RDW-SD (fL) $= 0.174 \times (\text{patient age})^{1.33} + 0.122 \times (\text{number of comorbidities with vascular risks})^{2.75} - 22.13$. The

TABLE 3 Relationships between vascular risk factors and RDW-SD at time of ITP diagnosis.

Variable	HR (95% CI)	*P*	Variable	PCC (95% CI)	*p*
Sex (female vs. male)	0.94 (0.75–1.27)	0.81	Age	0.79 (0.15–0.93)	0.02
History of cardiovascular disease	2.89 (1.56–5.67)	<0.01	WBC count at diagnosis	−0.037 (−0.49 to 0.24)	0.89
History of hypertension	1.56 (1.08–3.21)	0.03	Hb level at diagnosis	−0.20 (−0.67 to 0.12)	0.33
History of hyperlipidaemia	1.67 (1.11–3.33)	0.02	Reti count at diagnosis	0.12 (−0.24 to 0.45)	0.59
History of diabetes	2.22 (1.33–4.44)	<0.01	Platelet count at diagnosis	−0.12 (−0.44 to 0.21)	0.50
History of CKD	1.91 (1.18–3.24)	0.01	PDW value at diagnosis	0.21 (−0.12 to 0.56)	0.31
History of malignant tumor	2.57 (1.45–4.00)	<0.01	PAIgG value at diagnosis	0.05 (−0.25 to 0.30)	0.91
			LDH value at diagnosis	0.25 (−0.10 to 0.47)	0.12

Abbreviations: CI, Confidence interval; CKD, chronic kidney disease; Hb, hemoglobin; HR, hazard ratio; ITP, immune thrombocytopenic purpura; LDH, lactate dehydrogenase; PAIgG, platelet-associated IgG; PCC, Pearson correlation coefficient; PDW, platelet distribution width; RDW-SD, standard deviation of red blood cell distribution width; Reti, reticulocyte; WBC, white blood cell.

TABLE 4 Multivariate analyses.

	Bleeding		Thrombosis		Difficulty discontinuing corticosteroids		Infection	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
RDW-SD	2.39 (1.44–6.79)	0.028	2.22 (1.37–6.67)	0.030	1.90 (1.09–5.56)	0.045	1.95 (1.11–5.75)	0.040
Patient age	2.22 (1.33–6.67)	0.039	2.07 (1.24–6.33)	0.044	1.67 (1.00–5.20)	0.050	1.89 (1.08–5.33)	0.045
Number of comorbidities with vascular risk	1.67 (0.89–5.25)	0.27	1.58 (0.90–5.32)	0.37	1.24 (0.80–4.22)	0.39	1.20 (0.83–3.99)	0.44

Abbreviations: CI, Confidence interval; HR, hazard ratio; RDW-SD, standard deviation of red blood cell distribution width.

estimated values were correlated significantly with the actual values (contribution rate [R^2] = 0.78, $p = 0.03$, Figure 2). This approximate formula predicted high (≥ upper limit of normal range [51 fL]) RDW-SD values with an accuracy of 76.0% and low (< 51 fL) RDW-SD values with an accuracy of 90.0% ($p < 0.01$, Table 5), suggesting that the RDW-SD value at the time of diagnosis with ITP reflects a combination of vascular risks.

3.4 | Relationships between RDW-SD and clinical outcomes

Finally, we checked the relationships between the RDW-SD value at ITP diagnosis and several clinical outcomes (Table 6). The RDW-SD value had no association with resistance to first-line corticosteroid therapy or non-achievement of CR. However, RDW-SD was significantly associated with difficulty of corticosteroid discontinuation and incidences of bleeding, thrombosis, and infection. The result was consistent regardless of whether the thrombosis was venous or arterial.

4 | DISCUSSION

A reliable biomarker to predict the risks of bleeding and thrombosis well before the initiation of the first-line corticosteroid therapy is urgently required to optimize the treatment for ITP [13, 14, 17, 18]. In this retrospective cohort study, we found the following: (1) RDW-SD at the time of ITP diagnosis reflects several variables associated with vascular risks; (2) RDW at ITP diagnosis is a reliable and convenient biomarker to predict risks of bleeding and thrombosis; and (3) RDW at ITP diagnosis can predict the difficulty of corticosteroid discontinuation and risk of infection during the treatment for ITP.

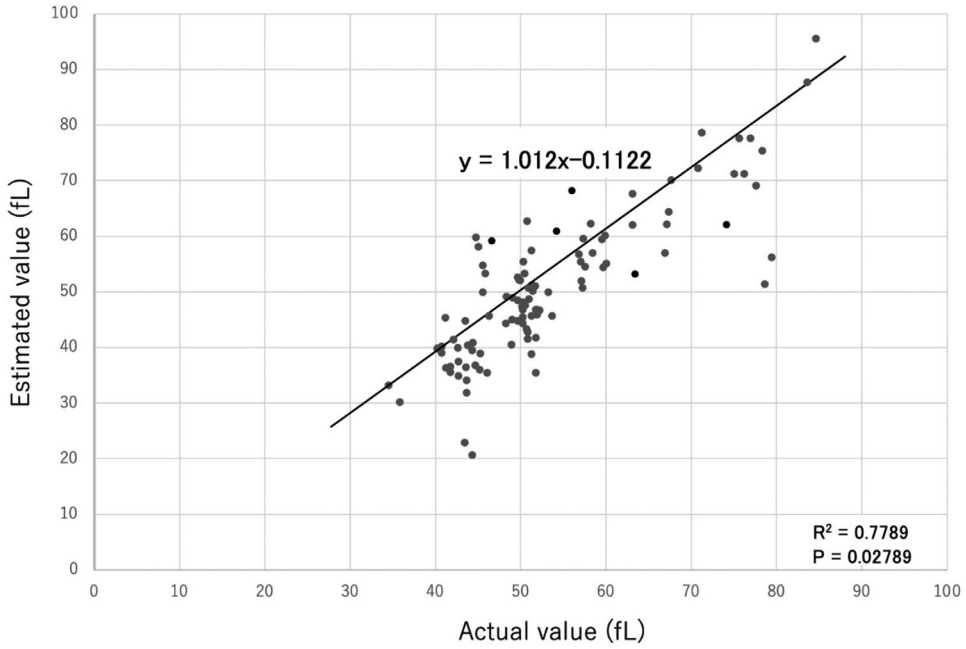

FIGURE 2 Correlation between actual and estimated values of RDW-SD. RDW-SD values measured before apheresis are plotted on the *x*-axis, and those estimated by using nine relevant parameters are shown on the *y*-axis. Each dot indicates one patient.

TABLE 5 Validation of estimated values of RDW-SD.

		Estimated value		
		<51 fL	≥51 fL	Total
Actual value	<51 fL	63 (90.0%)	12 (24.0%)	75 (62.5%)
	≥51 fL	7 (10.0%)	38 (76.0%)	45 (37.5%)
	Total	70 (100%)	50 (100%)	120 (100%)

Note: $p < 0.001$ (Fisher's test).

RDW is a readily measurable laboratory parameter of heterogeneity in red blood cell size [19–21]. RDW-SD is calculated from the diameter-of-erythrocyte distribution curve at 20% above baseline and is expressed in femtolitres [22–24]. Originally, RDW was used to evaluate anisocytosis of red blood cells and to differentiate causes of anemia [25–29]. Recently, however, RDW has been employed in various clinical fields. For instance, in cardiovascular disease, vascular endothelial damage causes elevated RDW [30–33]. A balance between endothelium-derived relaxing factors (nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor) and endothelium-derived contracting factors (superoxide anion, endothelin-1, and constrictive prostaglandins) is a key to the regulation of vascular function [34]. Disruption of this balance induces endothelial dysfunction [35]. Aging and chronic cardiometabolic disorders, such as hypertension, hyperlipidaemia, diabetes mellitus, CKD, and atherosclerotic vascular diseases are closely linked to endothelial dysfunction [36, 37]. Several researchers have hypothesized that endothelial dysfunction can lead to increased RDW by suppressing effective bone marrow erythropoiesis and thus increasing red blood cell variability [38–40]. Oxidative stress decreases erythrocyte survival and increases the numbers of circulating premature erythrocytes, resulting in anisocytosis and higher RDW [41–43]. The more severe the vascular endothelial injury, the more likely bleeding and thrombosis are to develop. Therefore, a high RDW is significantly associated with the risks of bleeding and thrombosis during the treatment for ITP.

Elevated RDW has been associated not only with vascular risks, but also with the prognosis and risks of complications of various cancers, such as breast, lung, and esophageal cancers [44–48]. Recently, RDW has been reported as a potentially useful biomarker to predict prognosis and complication risks in hematologic cancers, such as diffuse large B-cell lymphoma, primary central nervous system lymphoma, multiple myeloma and chronic myeloid leukemia [49–53]. Here, we have added to the role of RDW as a prognostic tool by showing that a high RDW is significantly associated with risks of bleeding and thrombosis, difficulty with corticosteroid discontinuation and infectious risks during the treatment for ITP.

TPO-RA and splenectomy are risk factors for thrombosis [8–10, 54]. To prevent thrombosis during the treatment for ITP, hematologists might hesitate to add TPO-RA or perform splenectomy after first-line corticosteroid monotherapy in patients with many vascular risks, instead continuing with corticosteroid therapy alone for a longer period. We speculate that this is why a high RDW is significantly associated with difficulty in discontinuing corticosteroids. Long-term corticosteroid administration causes several complications, such as infection, osteoporosis, and adrenal insufficiency [54–55]. We expect that this is why a high RDW is significantly associated with incidence of infection during the ITP treatment. From this point of view, the use of other treatment agents, such as fostamatinib and rituximab, might be good choices as second- or higher-line therapy for patients with high RDW at diagnosis. In addition, strict control of blood pressure,

TABLE 6 Relationships between RDW-SD and clinical outcomes.

	HR (95% CI)	*p*
Resistance to first-line corticosteroid therapy	1.19 (0.89–1.24)	0.78
Non-achievement of CR by corticosteroid monotherapy	1.12 (0.81–1.30)	0.89
Difficulty with corticosteroid discontinuation	2.22 (1.45–3.67)	0.01
Incidence of bleeding during ITP treatment	2.75 (1.89–4.44)	<0.01
Incidence of thrombosis during ITP treatment	2.67 (1.67–4.25)	< 0.01
Venous thrombosis	2.87 (1.98–4.67)	<0.01
Arterial thrombosis	2.46 (1.56–3.98)	<0.01
Incidence of infection through ITP treatment	1.78 (1.03–2.98)	0.04

Abbreviations: CI, Confidence interval; CR, complete response; HR, hazard ratio.

cholesterol, triglyceride, and blood-sugar level during the treatment for ITP might be important to reduce the risks of bleeding and thrombosis especially for the ITP patients with higher RDW values.

The limitations of our study include its single-center, retrospective design involving patients with heterogenous backgrounds and potential confounding factors that may have affected outcomes. Our study included only a small number of cases, so the ability to control for confounding variables and establish causality between RDW-SD and outcomes might be limited. Thus, we accounted for this limitation by the careful use of subgroup and multivariate analyses. In addition, this study focuses primary ITP patients treated based on the Japanese guidelines for the ITP management, which might differ from the standards or practices in other countries.

In summary, our study revealed that the RDW value at diagnosis with ITP integrates clinical variables associated with vascular risks and can be used as a convenient, useful biomarker to predict risks of bleeding and thrombosis, difficulty with corticosteroid discontinuation, and infection during treatment for ITP. Our results shed light on how RDW can be used to predict complications of the ITP treatment and will therefore help to optimize the management of ITP.

AUTHOR CONTRIBUTIONS

Naokazu Nakamura designed the research, organized the project, and performed statistical analyses. Ryo Ikunari, Yasuhiro Tanaka, Hiroko Tsunemine, and Nobuyoshi Arima interpreted data. All authors critically reviewed the draft and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interests.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available from the corresponding author upon request.

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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