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ORIGINAL ARTICLE

Criteria for low von Willebrand factor diagnosis and risk score to predict future bleeding

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Abstract

Background: Important diagnostic and clinical aspects of moderately reduced von Willebrand factor (VWF) levels are still unknown. There is no clear evidence which cutoff value (0.50 vs 0.60 IU/ml) should be used to diagnose "low VWF." Also, the incidence of bleeding after the diagnosis has been made, and risk factors for bleeding are unknown yet.

Objectives: To investigate the incidence of postsurgical bleeding, postpartum hemorrhage (PPH), and traumatic and spontaneous bleeding after low VWF diagnosis, and to develop a risk score to predict future bleeding.

Methods: We performed a cohort study in patients with historically lowest VWF levels of 0.31 to 0.60 IU/ml. Clinical data of patients were retrospectively collected.

Results: We included 439 patients with low VWF. During a follow-up of 6.3 ± 3.7 years, 259 surgical procedures, 81 deliveries, and 109 spontaneous and traumatic bleeding episodes were reported. The incidence of postsurgical bleeding was 2.7%, whereas 10% of deliveries was complicated by PPH. Overall, 65 patients (14.8%) had bleeding requiring treatment, which was not different between patients with historically lowest VWF levels of 0.31–0.50 and 0.51–0.60 IU/ml (p = .154). Age <18 years, abnormal bleeding score at diagnosis, and being referred for bleeding symptoms at the time of diagnosis were independent risk factors for bleeding during follow-up, and therefore included in the risk score.

Conclusions: The cutoff value of low VWF diagnosis should be set at 0.60 IU/ml. Furthermore, a risk score is developed to identify individuals with a high risk for bleeding after low VWF diagnosis.

KEYWORDS
diagnosis, hemorrhage, risk factors, Von Willebrand disease, Von Willebrand factor

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1 | INTRODUCTION

Von Willebrand factor (VWF) is a multimeric glycoprotein with an important role in primary hemostasis by binding platelets to subendothelial collagen at sites of vascular damage and by initiating platelet aggregation to form a platelet plug.[1–3] In addition, VWF is a carrier protein for coagulation factor VIII (FVIII), preventing its proteolytic degradation and thereby prolonging FVIII half-life.[1,3]

A deficiency or an abnormal function of VWF, which is prevalent in approximately 1% of the general population, may lead to bleeding symptoms.[4,5] Individuals with VWF levels below 0.30 IU/ml are diagnosed with von Willebrand disease (VWD).[1] Most patients with VWD have a significant bleeding phenotype and a *VWF* mutation, especially those with type 2 and type 3 VWD.[1] A milder decrease of VWF levels (i.e., levels of 0.31-0.50 IU/ml) does not always lead to bleeding symptoms because only a small fraction of individuals with such VWF levels have a significant bleeding phenotype.[2,5–8] As a consequence, it has been suggested that reduced VWF levels in the range of 0.31 to 0.50 IU/ml is a risk factor for bleeding and not a disease.[9,10] According to current guidelines individuals with VWF levels of 0.31 to 0.50 IU/ml and a significant bleeding phenotype are classified as "low VWF."[6–8]

Although several large studies have recently provided valuable insights on the pathophysiology, diagnosis, bleeding phenotype, and treatment outcomes of VWD patients, these aspects remain poorly understood in individuals with low VWF.[11–17] Most importantly, there is no clear evidence which cutoff value should be used to diagnose low VWF.[18] The most recommended cutoff value is 0.50 IU/ml,[8] although VWF levels in the range of 0.51 to 0.60 IU/ml may also contribute to bleeding.[19] Moreover, 0.60 IU/ml is in some laboratories the lower limit of normal and therefore used as cutoff value to diagnose low VWF. No studies have been performed yet to determine the difference in bleeding phenotype of individuals with VWF levels of 0.31 to 0.50 IU/ml and 0.51 to 0.60 IU/ml.[18] Second, the incidence of postsurgical bleeding, postpartum hemorrhage (PPH) and traumatic or spontaneous bleeding after diagnosis of low VWF are not known yet. It is also not known which factors are associated with the risk of these bleeding. Last, it is hard to predict which individuals with low VWF are at increased risk for bleeding and which individuals will almost never have bleeding episodes after they are diagnosed with low VWF.

Therefore, we investigated whether there is a difference in the bleeding phenotype of individuals with historically lowest VWF levels of 0.31 to 0.50 IU/ml and 0.51 to 0.60 IU/ml. Second, we investigated the incidence of postsurgical bleeding, PPH, and traumatic and spontaneous bleeding in individuals with low VWF after their initial diagnosis. We also studied which factors are associated with the risk of such bleeding. Last, we combined these risk factors to develop a risk score to predict which individuals with low VWF are at increased risk for future bleeding.

Essentials

- There is no clear evidence which cut-off value (0.50 vs 0.60 IU/ml) should be used to diagnose "low VWF."
- We performed a cohort study with a mean follow-up of 6.3 ± 3.7 years in patients with historically lowest VWF levels of 0.31–0.60 IU/ml.
- No difference was found in the bleeding phenotype of patients with historically lowest VWF levels of 0.31–0.50 and 0.51–0.60 IU/ml.
- A risk score is developed to identify individuals with a high, intermediate and low risk for bleeding after low VWF diagnosis.

2 | METHODS

2.1 | Setting and participants

We performed a retrospective cohort study from January 2007 to November 2019 at the Erasmus University Medical Center, Rotterdam, the Netherlands. All patients evaluated for the presence of a bleeding disorder at the outpatient department, with VWF antigen (VWF:Ag) and/or VWF activity (VWF:Act) and/or VWF collagen binding (VWF:CB) levels between 0.31 and 0.60 IU/ml measured at least at one time point between January 2007 and November 2019, were included. Patients with VWF:Ag and/or VWF:Act and/or VWF:CB ≤0.30 IU/ml ever measured, those with acquired VWD, and patients with concomitant bleeding disorder were excluded.

2.2 | Assessment methods

At inclusion, the bleeding phenotype of all individuals with VWF levels between 0.31 and 0.60 IU/ml was obtained by a consultant hematologist specializing in bleeding disorders. These data were used to calculate the ISTH-Bleeding Assessment Tool (ISTH-BAT).[20] In patients that were included before the ISTH-BAT was published, we have retrospectively calculated the ISTH-BAT based on the information reported in the electronic patient files. An abnormal ISTH-BAT is defined as a score of ≥3 in children, ≥4 in males, and ≥6 in females.[20,21]

Retrospective follow-up started at the moment of low VWF diagnosis and continued until November 2019. For each individual, we collected data on baseline characteristics, reason for consultation, family history of bleeding disorders, ISTH-BAT at diagnosis, and laboratory measurements. Furthermore, follow-up data on surgical procedures, pregnancies, deliveries, and incidence of spontaneous and traumatic bleeding were collected from electronic patient files.

2.3 | Laboratory measurements

Plasma levels of VWF:Ag, VWF:Act, VWF:CB, and FVIII activity (FVIII:C) were determined at the hemostasis laboratory of the Erasmus University Medical Center. Previous studies provide detailed information on blood sampling procedures and laboratory measurements.[16,22] Briefly, for VWF:Ag and VWF:CB, in-house enzyme-linked immunosorbent essays were used. Detection of VWF:Ag was performed using polyclonal rabbit anti-human VWF antibodies and horseradish peroxidase conjugated anti-human VWF antibodies (DakoCytomation, Glostrup, Denmark). For VWF:CB, collagen type 1 (Sigma-Aldrich, St Louis, MO) was used for capturing and horseradish peroxidase–conjugated anti-human VWF antibodies (DakoCytomation) for detection. Before 2012, VWF:Act was measured with the VWF:Ab assay (HemosIL VWF activity; Instrumentation Laboratory BV, Breda, the Netherlands), which used monoclonal antibodies against the GP1ba binding site of VWF, reflecting the binding activity of VWF to GP1ba.[22,23] From 2012 on, VWF:Act was measured with the VWF:GPIbM Innovance assay from Siemens on a Sysmex CS-5100. FVIII:C was measured using a one-stage clotting assay (TriniCLOT; bioMérieux, Marcy l'Etoile, France) on the Sysmex CS-5100 (Siemens). Multimeric patterns were evaluated with the use of low-resolution 0.9% agarose gel electrophoresis (Bio-Rad Laboratories) followed by capillary Western blotting. VWF multimers were classified as either absent, abnormal, or normal based on comparison with commercial reference plasma (normal reference plasma; Precision Biologic). Additional coagulation tests were measured with validated standard diagnostic assays.

2.4 | Definitions

Surgical procedures were defined as medical interventions that invade the body by cutting or puncturing the skin and/or by inserting instruments into the body, such as surgery, dental procedures, or invasive examinations.[23] Because there is a large variability in the bleeding risk of such interventions, we have classified the bleeding risk of each intervention based on previous literature.[24] Furthermore, major postsurgical bleeding was defined as bleeding requiring resurgery or blood transfusion, whereas minor postsurgical bleeding was defined as bleeding requiring additional tranexamic acid (TXA), desmopressin or VWF concentrates, or bleeding for which patients had to stay longer at the hospital or had to visit the outpatient department or emergency room of the Erasmus University Medical Center. PPH was defined as blood loss ≥500 mL within 24 hours' postpartum or bleeding for which curettage, additional TXA, desmopressin, or VWF concentrate was necessary. Severe PPH was defined as blood loss ≥1000 mL within 24 hours' postpartum.[25] Secondary PPH was defined as blood loss occurring between 24 hours' and 6 weeks' postpartum.[26] Peripartum blood loss was estimated by the obstetrician-gynecologist who supervised the delivery, as is routinely done in the Netherlands. Trauma was defined as an event for which patients contacted the outpatient department or emergency room of the Erasmus University Medical Center. Spontaneous or traumatic bleeding during follow-up was defined as bleeding for which patients contacted the outpatient department or ER. Last, bleeding requiring treatment was defined as bleeding treated with tranexamic acid (TXA), desmopressin, VWF containing concentrates, blood transfusion, (re)surgery, cauterization in case of epistaxis, suturing of wounds, hormonal therapy, or a hormone containing intrauterine device in case of menorrhagia and curettage in case of PPH.

2.5 | Statistical analyses

Categorical variables are presented as frequencies and percentages (*n*, %), whereas continuous variables are presented as mean (± standard deviation). Normality of data was assessed with histograms. Missing data were not replaced.

Parametric tests were used in case of analyzing more than 30 individuals or normal distributed data. An independent *t*-test or one-way analysis of variance was used to compare continuous variables between different groups. Differences in categorical data among different subgroups were analyzed using a chi-squared test. Kaplan-Meier analysis with log-rank test was performed to determine whether there was a difference in time to bleeding requiring treatment between categorical variables. Cox regression analysis was used to determine whether there was a difference in time to bleeding requiring treatment between continuous variables. For the association between hemostatic laboratory measurements and risk of bleeding requiring treatment, we have used the historically lowest levels as independent variables. To identify independent risk factors for bleeding requiring treatment, we performed a cox regression analysis with forward (Wald) method in which we included all variables that were significantly associated with bleeding requiring treatment in univariate analysis. Outcomes of Cox regression analysis are presented as hazard ratio followed by the 95% confidence interval (CI) and *p* value. Statistical analyses were performed using SPSS Statistics version 25 (IBM Corp.). A *p* value below .05 was defined as statistically significant.

3 | RESULTS

In our outpatient hemophilia treatment center, we identified 476 patients referred because of a personal bleeding diathesis, family history of VWD or low VWF, or incidentally found laboratory abnormalities, in whom laboratory assessment revealed VWF levels between 0.31 and 0.60 IU/ml from 2007 to November 2019. A concomitant bleeding disorder was present in 37 (7.8%) individuals, of whom 12 were carriers of hemophilia A, five had hemophilia A or B, 10 had a platelet function disorder, five had thrombocytopenia, and five had a rare bleeding disorder. These individuals were excluded from this study, and therefore we included 439 patients of whom 269 patients with historically lowest VWF levels between 0.31 and

0.50 IU/ml and 170 patients with historically lowest levels between 0.51 and 0.60 IU/ml (Table 1).

The reason for referral was a personal bleeding diathesis in 288 (65.6%) patients, a positive family history of VWD or low VWF in 138 (31.4%) patients and incidentally found laboratory abnormalities in 13 (3.0%) patients (Table 1). Mean age at diagnosis and inclusion in the study was 28.8 ± 17.7 years, and was lower in patients with historically lowest levels of 0.31 to 0.50 IU/ml (26.7 ± 17.3) compared with those with 0.51 to 0.60 IU/ml (32.1 ± 17.8, $p = .002$). Most patients were female (74.3%) and had blood group O (76.4%) (Table 1). The mean follow-up period after diagnosis was 6.3 ± 3.7 years. Figure 1 gives an overview of the number of patients with surgical procedures, deliveries, and traumatic and spontaneous bleeding during follow-up.

3.1 | Bleeding score at diagnosis

The mean ISTH-BAT bleeding score at diagnosis was 3.8 ± 3.0, and was abnormal in 163 individuals (37.1%). Individuals referred for a personal bleeding diathesis presented with a higher bleeding score at diagnosis (4.6 ± 2.8) compared with those referred because of a family history of VWD or low VWF (2.2 ± 2.7, $p < .001$). Additionally, the number of individuals with an abnormal bleeding score was 138 (47.9%) in those referred for a personal bleeding diathesis, whereas it was only 21 (15.2%) in those referred for a family history of VWD or low VWF, and four (30.8%) in those referred because of an incidentally found laboratory abnormality ($p < .001$). After adjustment for age and sex, individuals referred for a personal bleeding diathesis had a five times higher chance of presenting with an abnormal bleeding score compared with patients referred for family history of VWD or low VWF: odds ratio = 5.0 (3.0-8.4). The bleeding score was similar between patients with historically lowest VWF levels 0.31 to 0.50 IU/ml and 0.51 to 0.60 IU/ml, respectively 3.7 ± 3.0 vs 4.0 ± 2.9 ($p = .209$) (Table 1). Likewise, the number of individuals with an abnormal bleeding score was similar between patients with historically lowest VWF levels 0.31 to 0.50 IU/ml and 0.51 to 0.60 IU/ml, respectively 96 (35.7%) vs 67 (39.4%) ($p = .431$) (Table 1).

3.2 | Surgical procedures during follow-up

During the follow-up period of 6.3 ±3.7 (mean ± standard deviation) years, 259 surgical procedures were performed in 146 individuals. Of these procedures, 233 (90.0%) were preceded by prophylactic treatment, which was desmopressin and TXA in 105 procedures

TABLE 1 Baseline characteristics

	Historically Lowest VWF Levels			
	0.31-0.50 IU/ml *N* = 269	0.51-0.60 IU/ml *N* = 170	Total *N* = 439	*p* Value
Age at diagnosis (years)	26.7 ± 17.3	32.1 ± 17.8	28.8 ± 17.7	0.002
Female	193 (71.7%)	133 (78.2%)	326 (74.3%)	0.130
Blood group O	178 (77.4%)	103 (74.6%)	281 (76.4%)	0.547
BMI (kg/m^2)	23.2 ± 5.3	23.5 ± 5.2	23.3 ± 5.2	0.662
Reason for referral				
Bleeding diathesis	172 (63.9%)	116 (68.2%)	288 (65.6%)	0.473
Family history	90 (33.5%)	48 (28.2%)	138 (31.4%)	
Laboratory abnormality[a]	7 (2.6%)	6 (3.5%)	13 (3.0%)	
Historically lowest levels				
VWF:Ag (IU/ml)	0.51 ± 0.12	0.62 ± 0.11	0.55 ± 0.13	<0.001
VWF:Act (IU/ml)	0.47 ± 0.09	0.62 ± 0.08	0.53 ± 0.11	<0.001
VWF:CB (IU/ml)	0.55 ± 0.18	0.69 ± 0.16	0.60 ± 0.18	<0.001
FVIII:C (IU/ml)	0.78 ± 0.21	0.90 ± 0.21	0.83 ± 0.22	<0.001
PFA epi (seconds)	185 ± 48	168 ± 43	178 ± 47	0.001
PFA ADP (seconds)	151 ± 44	138 ± 31	147 ± 40	0.004
Bleeding score at diagnosis	3.7 ± 3.0	4.0 ± 2.9	3.8 ± 3.0	0.209
Abnormal bleeding score[b]	96 (35.7%)	67 (39.4%)	163 (37.1%)	0.431
Follow-up (years)	6.6 ± 3.7	5.9 ± 3.7	6.3 ± 3.7	0.068

Note: Data presented as mean ± standard deviation or number (%), unless otherwise specified.

Abbreviations: Act, activity; ADP, adenosine diphosphate; Ag, antigen; BMI, body mass index; CB, collagen binding; epi, epinephrine; FVIII:C, factor VIII activity; PFA, platelet function assay; VWF, von Willebrand factor.

[a]Incidentally found for instance with PFA screening before surgery.

[b]Abnormal ISTH-BAT is defined as ≥3 in children, ≥4 in males, and ≥6 in females.

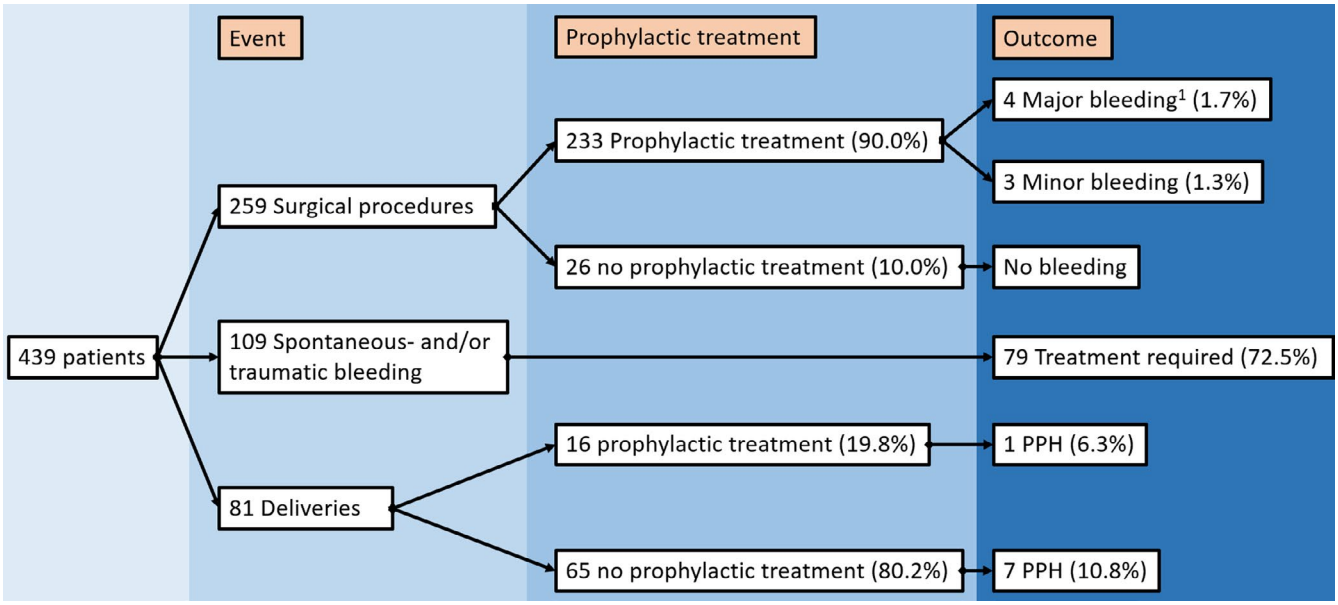

FIGURE 1 Overview of surgical procedures, bleeding, and child deliveries during follow-up. PPH, postpartum hemorrhage. [1]Bleeding requiring resurgery or blood transfusion

(45.1%), desmopressin alone in 47 procedures (20.2%), VWF containing concentrates with or without TXA in 62 procedures (26.6%), and TXA alone in 15 procedures (6.4%). Major bleeding, defined as bleeding requiring resurgery or blood transfusion, occurred in four procedures (1.5%), whereas minor bleeding occurred in three procedures (1.2%). Table 2 shows detailed information of the seven patients with a postsurgical bleeding. Two of the four individuals with a major bleeding had important comorbidities and an American Society of Anesthesiologists Physical Status score of 4. Both patients underwent major surgery. Moreover, one of them restarted clopidogrel after surgery and before the occurrence of bleeding. Furthermore, a young child with persistent bleeding within 2 hours after adenotonsillectomy needed resurgery because of a clear anatomical bleeding focus, which was effectively treated with thermal coagulation. The last patient with a major bleeding, which occurred 8 days after facial nerve reconstruction, did not have a local cause for bleeding. Likewise, no cause for bleeding was identified in the three patients with minor bleeding.

Last, in 233 procedures that were preceded by prophylactic treatment, none of the patients developed side effects of hemostatic treatment, such as venous or arterial thrombosis.

3.3 | Postpartum hemorrhage during follow-up

Fifty-six women had 81 deliveries during follow-up. In 16 deliveries (19.8%) prophylactic treatment was given at delivery. Overall, eight deliveries (9.9%) were complicated by a PPH, of which one occurred despite prophylactic treatment (1/16: 6.3%) and seven in deliveries in which no prophylactic treatment was given (7/65: 10.8%) (p = .587, Figure 1). The woman with PPH despite prophylactic treatment, received platelet transfusion and TXA as prophylaxis, because she had experienced PPH in a prior delivery despite normalization of VWF levels in the third trimester. Table 3 shows the characteristics of women with PPH. All women with PPH had normalized VWF levels in the third trimester (i.e., VWF:Act and VWF:Ag >1.00 IU/ml). Four women had primary PPH, three had secondary PPH, and one had both primary and secondary PPH. Interestingly, all women with PPH of whom obstetric risk factors during delivery could be retrieved from the patient files (n = 7), had a retained placenta. Furthermore, five of eight women (62.5%) who had a PPH during follow-up had a history of PPH before diagnosis of low VWF, whereas in women who did not have PPH during follow-up only 12 of 48 (25.0%) had a history of PPH before diagnosis (p = 0.047).

3.4 | Spontaneous and traumatic bleeding during follow-up

During follow-up, 109 spontaneous and traumatic bleeding episodes occurred in 71 individuals. Treatment such as hemostatic treatment, blood transfusion, cauterization for epistaxis, suturing of wounds, hormonal therapy, or intrauterine device for menorrhagia was required in 79 spontaneous and traumatic bleeding events, which occurred in 53 patients. Thirty-seven patients had a spontaneous bleeding for which they required treatment, whereas 13 patients had traumatic bleeding and three had both spontaneous and traumatic bleeding during follow-up. The type of bleeding for which most patients needed treatment during follow-up was menorrhagia (Figure 2). Twenty-five women received treatment for menorrhagia, which were hormonal therapy alone, TXA alone, hormonal therapy and TXA combined, desmopressin, or blood transfusion in one woman. Nine patients received treatment because of epistaxis, five because of gastrointestinal bleeding and

TABLE 2 Patients with postsurgical bleeding during follow-up

Sex	Age[a]	VWF	BS	ASA	Type of Surgery	VWF Preoperatively[c]	Prophylactic Treatment	Type of Bleeding	Classification of Bleeding	Time of Bleeding	Treatment
F	23	≤0.50	4	4	CABG	VWF:Ag 0.69 VWF:Act 0.68 VWF:CB 0.69 FVIII:C 1.08	Desmopressin 1 hour before surgery	Pericardial clots causing heart tamponade and drop of hemoglobin	Major	After 4 days	3 PCs, resurgery to remove clots, desmopressin
M	21	≤0.50	3	2[b]	Diagnostic excision of atypical naevus (1 cm) right knee	VWF:Ag 0.76 VWF:Act 0.63 FVIII:C 0.45	Desmopressin 1 hour before surgery, TXA 7 days	Presented at ER with persistent wound bleed	Minor	After 2 days	Wound closure strip
F	8	≤0.50	0	2[b]	Adenotonsillectomy	VWF:Ag 0.58 VWF:Act 0.55 VWF:CB 0.45 FVIII:C 1.17	Desmopressin 1 hour before surgery, TXA 7 days	Persistent bleeding on recovery room because of clear bleeding focus	Major	Within 2 hours	Resurgery with cauterization of bleeding focus, desmopressin 1 day
F	43	≤0.50	9	2	Laparoscopic myoma enucleation and ovarian cyst excision	VWF:Ag 0.53 VWF:Act 0.65 VWF:CB 0.64 FVIII:C 0.90	Haemate-P before and 3 days postsurgery, TXA 7 days	Presented at ER with vaginal blood loss	Minor	After 4 days	Desmopressin 2 days
M	36	≤0.50	4	2	Reconstruction facial nerve paresis	VWF:Ag 0.64 VWF:Act 0.60 VWF:CB 0.51 FVIII:C 1.05	Haemate-P before until 3 days postsurgery	Presented at ER with spontaneous cheek bleeding	Major	After 8 days	Haemate-P 7 days, surgical relieve, TXA 10 days
F	78	≤0.50	6	4	Open reposition and internal fixation (ORIF) of femur	VWF:Ag 0.90 VWF:Act 1.07 VWF:CB 1.04 FVIII:C 1.23	Haemate-P before and 2 times daily postsurgery	1.5 L blood loss during surgery and drop of hemoglobin postsurgery	Major	During surgery	5 PC, 2 FFP, Haemat-P until 3 days postsurgery
M	21	≤0.50	7	2	Le Fort 1 distraction and three molar extractions	VWF:Ag 0.61 VWF:Act 0.65 VWF:CB 0.59 FVIII:C 0.69	Desmopressin 1 hour before, 12 and 24 hours after surgery. TXA 7 days	Persistent nose bleed night after surgery	Minor	Within 12 hours	Higher dose desmopressin once

Abbreviations: Act, activity; Ag, antigen; ASA, American Society of Anesthesiologists Physical Status; CABG, coronary artery bypass grafting; CB, collagen binding; ER, emergency room; FFP, fresh frozen plasma; FVIII:C, factor VIII activity; PC, packet cells; TXA, tranexamic acid; VWF, von Willebrand factor.

[a]At the time of surgery.

[b]Without VWD ASA score would be 1.

[c]IU/ml. BS bleeding score.

TABLE 3 Women with postpartum hemorrhage during follow-up

Age[a]	BS	Prior PPH	Prior HMB	GxPx	Birth Mode	VWF	VWF Third Trimester	Prophylactic Treatment	Type of PPH	Blood Loss	Obstetric Risk Factors	Intervention
34	3	Yes	No	G2P0	Vaginal	0.51-0.60	VWF:Ag 1.51 VWF:Act 1.10	None	Primary	2500 mL	Retained placenta and uterine atonia	Manual removal of placenta (anesthesia), curettage and 2PCs and 1FFP.
32	8	No	No	G2P1	Vaginal	0.51-0.60	VWF:Ag 1.56 VWF:Act 1.77	None	Primary	1700 mL	Retained placenta and uterine atonia	Oxytocin, Sulprostone, Curettage with echography (anesthesia), Bakri balloon
20	4	No	Yes	G1P0	Vaginal	0.31-0.50	VWF:Ag 1.22 VWF:Act 1.01	None	Secondary	Persistent until 1 month	Unknown	Curettage
26	4	Yes	Yes	G2P1	Vaginal	0.31-0.50	VWF:Ag 1.51 VWF:Act 1.07	Platelet transfusion, TXA	Primary	2000 ml	Retained placenta	Curettage
34	1	No	No	G3P2	Cesarean section	0.31-0.50	VWF:Ag 1.41 VWF:Act 1.31	None	Secondary	After 2 weeks heavy blood loss	Retained placenta	Manual removal of placenta (anesthesia), TXA, desmopressin
30	3	Yes	No	G4P2	Vaginal	0.31-0.50	VWF:Ag 1.73 VWF:Act 1.84	None	Primary + secondary	3000 ml during delivery, after 2 weeks heavy blood loss	Retained placenta 2 times, uterine atonia	Sulprostone, 2 times manual removal of placenta (anesthesia), Bakri balloon, 6PCs, TXA
29	7	Yes	No	G4P1	Vaginal	0.31-0.50	VWF:Ag 1.68 VWF:Act 1.42	None	Primary	2100 ml	Retained placenta	Curettage (anesthesia), desmopressin
33	5	Yes	Yes	G3P2	Vaginal	0.51-0.60	VWF:Ag 3.18 VWF:Act 2.83	None	Secondary	After 4 weeks heavy blood loss	Retained placenta	Curettage (anesthesia), platelet transfusion.

Abbreviations: Act, activity; Ag, antigen; BS, bleeding score; FFP, fresh frozen plasma; GxPx, number of gravida and para; HMB, heavy menstrual bleeding; PC, packet cell; PPH, postpartum hemorrhage; TXA, tranexamic acid; VWF, von Willebrand factor.

[a]At delivery.

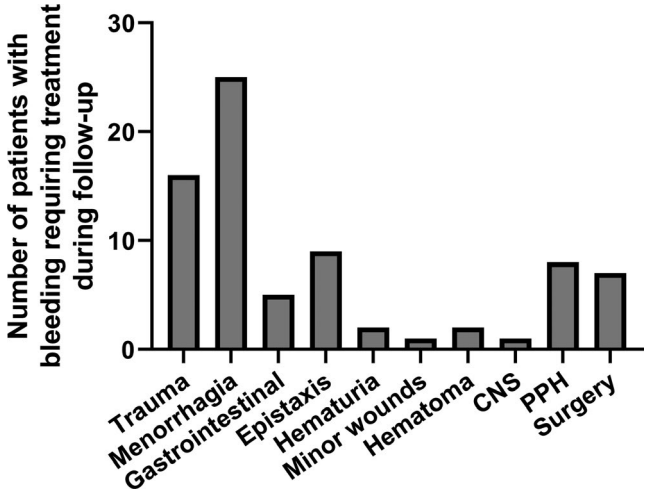

FIGURE 2 Number of patients with bleeding requiring treatment during follow-up. CNS, central nervous system; PPH, postpartum hemorrhage

two because of hematuria (Figure 2). Hematoma, bleeding from wounds, and central nervous system bleeding requiring treatment each occurred in a single patient (Figure 2). Spontaneous and traumatic bleeding requiring treatment was observed in 43 (14.9%) patients originally referred for bleeding, nine (6.5%) patients originally referred because of family history of VWD or low VWD and two (15.4%) patients referred because of an incidentally found laboratory abnormality (p = .044). There was no significant difference in the number of patients with spontaneous or traumatic bleeding during follow-up between patients with historically lowest VWF levels 0.31 to 0.50 IU/ml and 0.51 to 0.60 IU/ml, respectively, 38 patients (14.1%) vs 16 patients (9.4%), p = .143.

3.5 | Risk factors for bleeding requiring treatment during follow-up

Overall, only 65 of 439 patients (14.8%) had a bleeding episode (surgical, PPH, and spontaneous and traumatic bleeding combined) requiring treatment during the mean follow-up of 6.3 ± 3.7 years. This resulted in an incidence of bleeding requiring treatment of 0.5 ±1.9 per patient per decade. There was no difference in incidence of bleeding requiring treatment between patients with historically lowest VWF levels 0.31 to 0.50 IU/ml and 0.51 to 0.60 IU/ml (p = .154, Figure 3A). Also, no difference in risk of bleeding requiring treatment was observed between men and women (p = .752, Figure 3B). Although women had more often sex-specific bleeding such as menorrhagia and PPH during follow-up, men had more often traumatic bleeding requiring treatment compared with women, respectively, 8.0% of men vs 2.1% of women (p = .008). Remarkably, blood group non-O was associated with a higher risk of bleeding requiring treatment during follow-up (p = .044, Figure 3C), whereas patients younger than 17 years at diagnosis also had a higher risk of bleeding requiring treatment during follow-up compared to patients age 40 years or older (i.e., quartile 1 vs quartile 4, p = .041, Figure 3D). Furthermore, bleeding score at diagnosis (hazard ratio [HR] = 1.08 increase per point; 95% CI, 1.01-1.17; p = .032) and an abnormal bleeding score at diagnosis were also associated with a higher risk of bleeding requiring treatment during follow-up (p = .001, Figure 3E). Last, patients referred because of a personal bleeding diathesis had a higher risk of bleeding requiring treatment during follow-up compared with patients referred because of family history (p = .001, Figure 3F).

3.6 | Hemostatic laboratory measurements and risk of bleeding requiring treatment

Of all hemostatic laboratory measurements, we found that higher VWF:CB/VWF:Ag ratio (continuous variable) was associated with a lower risk of bleeding requiring treatment during follow-up: HR = 0.27 (95% CI, 0.10-0.76; p = .013; Table S1). There was also a clear difference in risk of bleeding requiring treatment between patients VWB:CB/VWF:Ag in the first quartile compared with those in the fourth quartile (p = .039).

3.7 | Independent risk factors for bleeding requiring treatment

To identify independent risk factors for bleeding requiring treatment in individuals with low VWF, we performed a Cox regression analysis with forward (Wald) method in which we included blood group, age at diagnosis, bleeding score at diagnosis, and reason for referral as independent variables. We found that referral for a personal bleeding diathesis, younger age at diagnosis, and an abnormal bleeding score at diagnosis were strong independent risk factors for bleeding requiring treatment during follow-up, respectively HR = 2.32 (95% CI, 1.16-4.63; p = .017), HR = 1.18 (95% CI, 1.01-1.38; p = .036), and HR = 1.77 (95% CI, 1.04-3.01; p = .036).

3.8 | Risk score to identify individuals with increased risk for bleeding requiring treatment

We combined the risk factors described previously to develop a risk score to identify low VWF patients with an increased risk for bleeding requiring treatment after diagnosis (Table 4). Individuals with a total risk score of 0 or 1 are classified as low risk, those with a total score of 2 are classified as intermediate risk, and those with a total risk score 3 to 5 are classified as high risk. The risk score performed excellently to distinguish in risk for bleeding requiring treatment between low-, intermediate-, and high-risk patients with low VWF (p < .001, Figure 4). The number of patients with bleeding requiring treatment was 8/126 (6.3%) in individuals with low-risk, 18/143 (12.6%) in intermediate-risk, and 39/170 (22.9%) in high-risk patients (p < .001, Figure 4A). Likewise, the

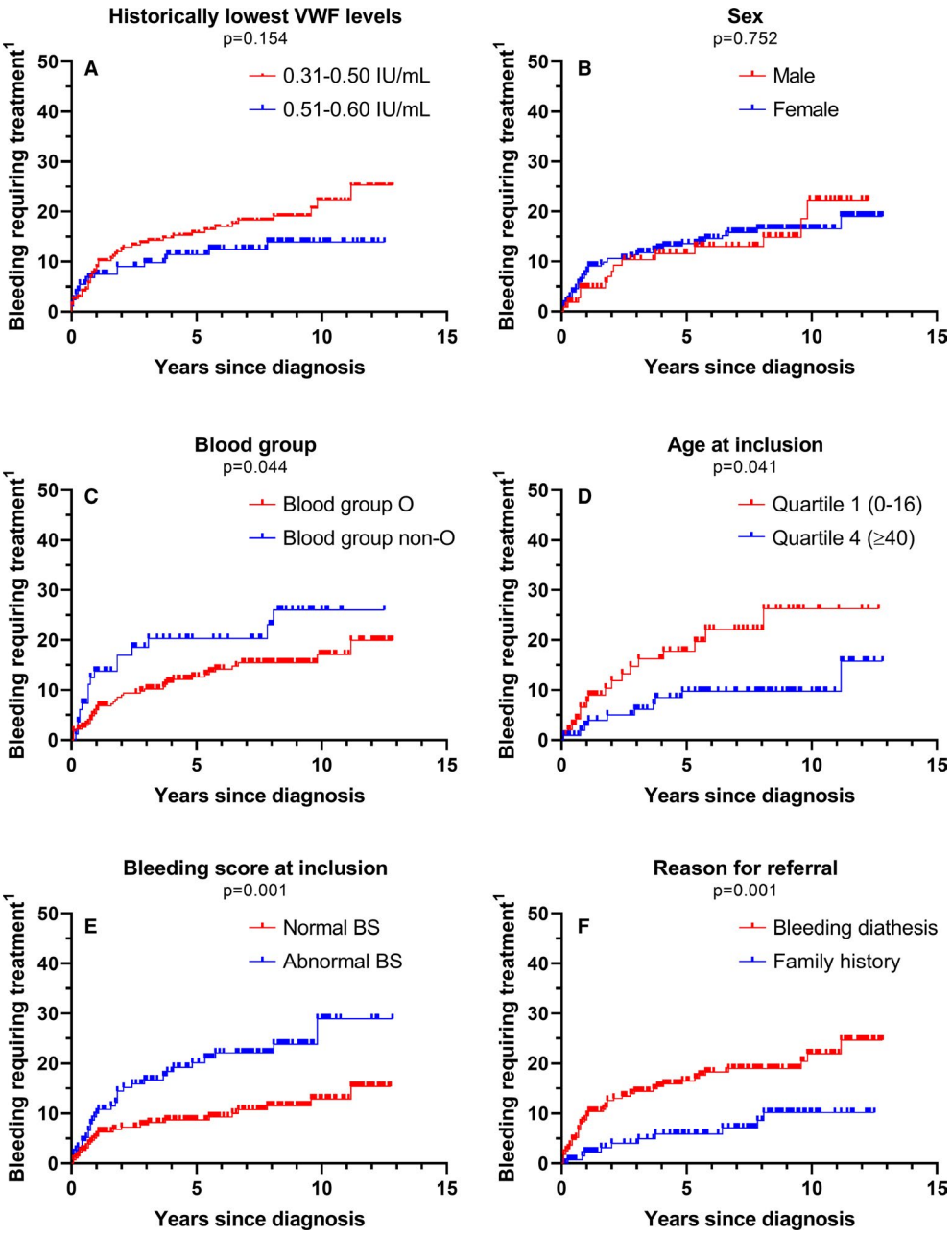

FIGURE 3 Risk factors for bleeding requiring treatment during follow-up. Results are presented as Kaplan-Meier curves. [1]Percentage of patients with a bleeding requiring treatment during follow-up. BS, bleeding score; VWF, von Willebrand factor

TABLE 4 Risk score to identify the bleeding-requiring-treatment risk of patients with low VWF

	Risk Score
Age <18 years at diagnosis	1
Abnormal bleeding score at diagnosis	2
Referred for personal bleeding diathesis	2

Note: Total risk score of 0-1: low risk. Total risk score of 2: intermediate risk. Total risk score of 3-5: high risk.

incidence of bleeding requiring treatment per patient per decade was 0.22 ± 1.08 in low-risk, 0.28 ± 1.25 in intermediate-risk, and 0.87 ± 2.61 in high-risk individuals (p = .004, Figure 4B).

4 | DISCUSSION

In this large retrospective cohort study in patients with low VWF, we found no difference in the bleeding phenotype of patients with historically lowest VWF levels between 0.31 to 0.50 IU/ml and 0.51 to 0.60 IU/ml. Second, we observed that prophylactic treatment during surgical procedures were effective in preventing bleeding and safe, as evidenced by a low rate of postsurgical bleeding and absence of side effects. Furthermore, 15% of patients required treatment for bleeding after diagnosis of low VWF, during an average follow-up of 6 years. Risk factors that were independently associated with bleeding requiring treatment during follow-up were younger age at

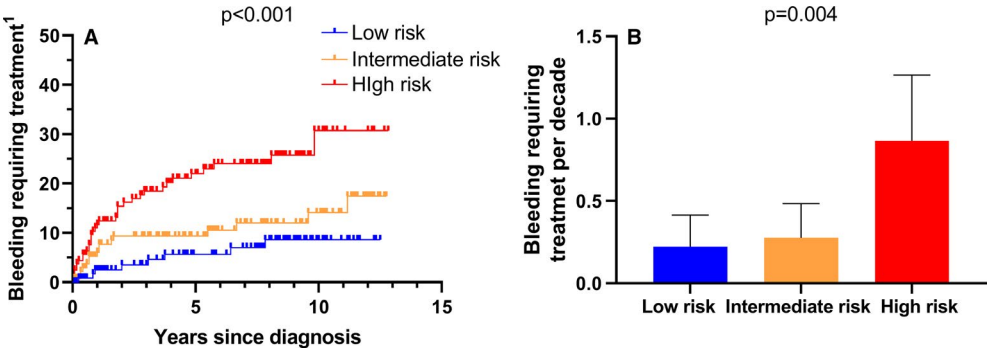

FIGURE 4 The risk score performs excellent in identifying individuals with low VWF with an increased risk for bleeding requiring treatment. (A) Kaplan-Meier curve of [1]percentage of patients with a bleeding requiring treatment during follow-up. (B) Bleeding requiring treatment rate per patient per decade. VWF, von Willebrand factor

diagnosis, abnormal bleeding score at diagnosis and referral for personal bleeding diathesis. Based on these factors, we developed a risk score to identify low VWF patients with high, intermediate, and low risk for future bleeding requiring treatment.

The cutoff value for diagnosing low VWF is still debated in recent literature.[19] In laboratories with 0.60 IU/ml as the lower limit of normal VWF levels, our results support a cutoff value of 0.60 IU/ml for low VWF diagnosis, and suggest that there should be no distinction in the management of individuals with historically lowest VWF levels 0.31 to 0.50 IU/ml and 0.51 to 0.60 IU/ml because the bleeding phenotype of both groups is similar. Correctly defining individuals with low VWF is essential because diagnosis or rejection of low VWF diagnosis has not only major consequences for the index patient in case of future interventions, pregnancies, deliveries, and management of future bleeding, but also for their family members because they are often analyzed when an index patient is identified. Accordingly, in the LoVIC study, no difference was found in bleeding score between individuals with VWF levels 0.30 to 0.39 IU/ml compared with those with VWF levels 0.40 to 0.50 IU/ml.[6,8] Together with the results of our current study, this suggests that there is no critical VWF level in respect to bleeding risk, at least not in the range of 0.31 to 0.60 IU/ml. In line, from all VWF laboratory parameters, only historically lowest VWF:CB/VWF:Ag ratio was associated with the bleeding risk during follow-up in the current study. This is probably explained by the fact that lower VWF:CB is associated with a reduction of high molecular weight VWF multimers, which may lead to a lower hemostatic potential.[27,28]

Fifteen percent of all individuals with low VWF experienced a bleeding episode requiring treatment during an average of 6 years after they were diagnosed with low VWF. Therefore, we developed a risk score to distinguish individuals with the highest risk for future bleeding from those with an intermediate risk and low risk. In adults with VWD, it was previously shown that a bleeding score above 10 is predictive for future bleeding.[29] In our current study we found that an abnormal bleeding score at diagnosis combined with referral for bleeding and age younger than 18 years at diagnosis, were strongly associated with the risk for future bleeding. A benefit of this risk score is that it includes all individuals with historically lowest VWF levels between 0.31 and 0.60 IU/ml, irrespective of their clinical features and reason for referral. For instance, individuals with levels of 0.31 to 0.60 IU/ml without a significant bleeding phenotype are in this risk score classified as individuals with low risk for bleeding. Likewise, those with levels 0.31 to 0.60 IU/ml and a significant bleeding phenotype are classified as intermediate or high risk based on their risk score. Nevertheless, it should be noted that in all included patients, current guidelines for prophylactic treatment during interventions and pregnancies were followed, and therefore the purpose of this risk score is not to determine the need for prophylactic treatment, but to make physicians and patients aware of the severity of bleeding risk in an individual. Future studies are needed to validate this risk score in other cohorts of individuals with low VWF.

The incidence of postsurgical bleeding was 2.7% after individuals were diagnosed with low VWF and 90% of procedures were preceded by prophylactic treatment. It is hard to compare this percentage with the incidence rate of postsurgical bleeding in the general population, because the bleeding rate highly depends on the type of surgery. In the general population, the incidence of postsurgical bleeding is estimated to be about 2% to 5%, dependent on the type of surgery.[30–32] Therefore, it seems like postsurgical bleeding does not occur more frequent in individuals with low VWF after their diagnosis. This can be explained by the fact that individuals with low VWF are closely monitored during surgical procedures, and prophylactic treatment is administered if deemed necessary based on VWF levels before surgical procedure, type of surgery, and concomitant risk factors for bleeding. Furthermore, in the general population it is known that 75% to 90% of intraoperative and early postoperative bleeding are due to technical, surgical factors.[33] Therefore, this should also not be neglected as potential risk factor for postsurgical bleeding in individuals with low VWF. Indeed, three of the four major postsurgical bleeding events in our cohort were associated with comorbidities, high-risk surgery, and surgical factors. Last, we found that prophylactic treatment for surgery was not complicated by side effects such as thrombosis, suggesting that prophylactic treatment based on current guidelines is safe in these individuals.

The incidence of PPH was 10% and the incidence of severe PPH was 6% during follow-up, despite management of pregnant women according to current guidelines and giving prophylactic treatment if needed. Both the incidence of PPH and severe PPH seemed to be higher in our cohort of women with low VWF compared with the general population, in which the incidence of PPH is about 1% to 4.5%.[25,34,35] Incidence of PPH during follow-up was lower in women with low VWF compared with those reported in a retrospective cohort study in women with VWD, who had a PPH incidence of 34%.[36] However, the incidence of severe PPH was comparable between women with low VWF and VWD, which was in both studies 8%.[36–38] Likewise, in parous women, the percentage of self-reported PPH during a lifetime was 63.5% in low VWF patients in the LoVIC study, whereas this number was 51% in VWD patients in the WiN study.[39,40] This suggests that the self-reported incidence of PPH during a lifetime is comparable between women with low VWF and VWD.[39,40] Furthermore, in the current study, we found that prior PPH was a risk factor for future PPH in women with low VWF. Also, in seven of eight women with PPH, we were able to obtain detailed information about obstetric risk factors, and found that all these women had a retained placenta, whereas in the general population, only 20% of women with PPH have a retained placenta.[35] Both prior PPH and retained placenta were in the general population also identified as important risk factors for future PPH.[35] Furthermore, a retained placenta is in the general population only present in 1% to 3% of all deliveries, whereas in our cohort the incidence of retained placenta was 9%.[34,35,41] Future studies should systematically investigate the incidence of PPH and its association with obstetric risk factors in women with low VWF.

The most important limitation of this study is the retrospective design. However, being aware of this limitation, we mainly focused on clinically relevant bleeding for which patients needed treatment and contacted our center. Because current national guidelines in the Netherlands recommend the treatment of inherited bleeding disorders to take place at a Hemophilia Treatment Center, we consider the data on bleeding requiring treatment to be reliable. Moreover, prospective studies on this subject are probably not feasible, because of the low incidence of bleeding requiring treatment one may either need thousands of patients or a very long follow-up to include enough "events" to have sufficient power to draw conclusions from such a study. In our current study, we included 439 patients and followed them up for an average of 6.3 years, resulting in 2766 patient-years of follow-up. During this follow-up period, 94 events (i.e., bleeding requiring treatment) occurred, which was sufficient to answer the predefined primary and secondary research questions. We do acknowledge that the risk of bleeding episodes that do not require treatment cannot be reliably obtained from a retrospective study because most of those bleeding episodes are not communicated by patients to the hospital. Therefore, numbers on bleeding that did not require treatment may be underestimated and prospective studies are needed to investigate those bleeding. Furthermore, we acknowledge that our study population of low VWF patients referred to our tertiary center, is a selected group and therefore not comparable with individuals with low VWF in the general population, most of whom do not have an increased bleeding phenotype.

To conclude, the results of this study suggest that in laboratories with 0.60 IU/ml as the lower limit of normal VWF levels there should be no distinction in the management of individuals with historically lowest VWF levels of 0.31 to 0.50 IU/ml and 0.51 to 0.60 IU/ml. Therefore, the cutoff value of diagnosing low VWF should be set at 0.60 IU/ml in these laboratories. Furthermore, the risk score developed in the current study may assist in the management of individuals with low VWF, to identify patients with high, intermediate, and low risk for future bleeding.

DATA SHARING STATEMENT

Original data can be obtained by sending an e-mail to the corresponding author (f.leebeek@erasmusmc.nl).

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CONFLICTS OF INTEREST

Dr. Atiq received the CSL Behring-professor Heimburger Award 2018 and a travel grant from Sobi. Dr. Cnossen has received grants from governmental research institutes, such as the Dutch Research Institute (NWO), ZonMW, Innovation fund, NWO-NWA, and unrestricted investigator-initiated research grants as well as educational and travel funding from various companies over the years (Pfizer, Baxter/Baxalta/Shire, Bayer Schering Pharma, CSL Behring, Sobi Biogen, Novo Nordisk, Novartis, and Nordic Pharma), and has served as a member on steering boards of Roche and Bayer. Dr. Leebeek received research support from CSL Behring and Shire/Takeda for performing the WiN study; is a consultant for uniQure, BioMarin, Novo Nordisk, and Shire/Takeda, the fees of which go to the institution; and has received a travel grant from Sobi. He is also a DSMB member for a study by Roche.

AUTHOR CONTRIBUTIONS

Ferdows Atiq and Esmee Wuijster designed the study, collected data, performed statistical analysis, interpreted data, and wrote the manuscript. Moniek P. M. de Maat, Marieke J. H. A. Kruip, and Marjon H. Cnossen interpreted data and critically revised the manuscript. Frank W. G. Leebeek designed the study, interpreted data, and critically revised the manuscript. All authors gave their consent to the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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