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ORIGINAL ARTICLE

Mitral regurgitation is associated with similar loss of von Willebrand factor large multimers but lower frequency of anemia compared with aortic stenosis

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Abstract

Background: Various cardiovascular diseases cause acquired von Willebrand syndrome (AVWS), which is characterized by a decrease in high-molecular-weight (large) von Willebrand factor (VWF) multimers. Mitral regurgitation (MR) has been reported as a cause of AVWS. However, much remains unclear about AVWS associated with MR.

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Objectives: To evaluate VWF multimers in MR patients and examine their impact on clinical characteristics.

Methods: Moderate or severe MR patients (n = 84) were enrolled. VWF parameters such as the VWF large multimer index (VWF-LMI), a quantitative value that represents the amount of VWF large multimers, and clinical data were prospectively analyzed.

Results: At baseline, the mean hemoglobin level was 12.9 ± 1.9 g/dL and 58 patients (69.0%) showed loss of VWF large multimers defined as VWF-LMI < 80%. VWF-LMI in patients with degenerative MR was lower than in those with functional MR. VWF-LMI appeared to be restored the day after mitral valve intervention, and the improvement was maintained 1 month after the intervention. Seven patients (8.3%) had a history of bleeding, 6 (7.1%) of whom had gastrointestinal bleeding. Gastrointestinal endoscopy was performed in 23 patients (27.4%) to investigate overt gastrointestinal bleeding, anemia, etc. Angiodysplasia was detected in 2 of the 23 patients (8.7%).

Conclusion: Moderate or severe MR is frequently associated with loss of VWF large multimers, and degenerative MR may cause more severe loss compared with functional MR. Mitral valve intervention corrects the loss of VWF large multimers. Gastrointestinal bleeding may be relatively less frequent and hemoglobin level remains stable in MR patients.

KEYWORDS
angiodysplasia, gastrointestinal hemorrhage, mitral valve insufficiency, von Willebrand diseases, von Willebrand factor

Essentials

- Mitral regurgitation is known to cause acquired von Willebrand syndrome.
- We examined von Willebrand factor (VWF) large multimers in patients with moderate or severe mitral regurgitation.
- Loss of VWF large multimers was common, although the frequency of anemia was not high.
- Mitral valve intervention immediately ameliorated the loss of VWF large multimers.

1 | INTRODUCTION

von Willebrand factor (VWF) is a large multimeric glycoprotein that plays an important role in hemostasis and thrombosis. VWF is produced as a huge multimer and then cleaved in a shear stress–dependent manner by the metalloprotease ADAMTS-13 (a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13) [1–3]. Among various sizes of VWF multimers, the high-molecular-weight (large) multimers play an important role in hemostasis [4]. In some cardiovascular diseases, unphysiological high shear stress is generated in the bloodstream, which causes excessive cleavage of VWF into smaller multimers. As a result, the loss of large multimers leads to a hemostatic disorder known as acquired von Willebrand syndrome (AVWS).

It is well known that aortic stenosis (AS) that accompanies excessive high shear stress at the stenotic valve is frequently associated with gastrointestinal bleeding, a condition designated as Heyde syndrome [5–7]. The bleeding is typically attributed to gastrointestinal angiodysplasia, fragile and abnormal vessels immediately beneath the mucosa [8]. In addition to AS, hypertrophic obstructive cardiomyopathy [9], pulmonary hypertension [10], congenital structural heart diseases [11], mitral regurgitation (MR) [12–16], and mechanical circulatory support [17,18] have also been previously reported to cause AVWS.

MR has been reported as a cause of AVWS in several studies [12–16]. Blackshear et al. [12] reported that the VWF activity and amount of VWF large multimers decreased according to the severity of MR and that a high rate (41.5%) of patients had a bleeding history. Nevertheless, MR is not considered to be associated with bleeding in clinical settings in general. In our experience, the frequency of gastrointestinal bleeding in MR is much lower than that in AS. Blackshear et al. [12] also reported that VWF function improved significantly in all patients after open-heart surgery with mitral valve plasty or mitral valve replacement, while Meindl et al. [13] showed that VWF activity/antigen ratios in patients who underwent transcatheter mitral valve repair did not improve 4 weeks after the procedure.

Thus, further studies would be required for the characterization of MR-associated loss of VWF large multimers, especially to elucidate the association with bleeding and the effect of mitral valve intervention. Here, we systematically investigated VWF multimers by using a quantitative VWF multimer analysis in a multicenter prospective study of patients with moderate or severe MR.

2 | METHODS

2.1 | Study population

The AVeC (acquired von Willebrand syndrome co-existing with cardiovascular diseases) Study was a multicenter prospective study designed to investigate the clinical features and pathophysiology of AVWS in patients with cardiovascular disease, such as AS and MR, and in those treated with mechanical circulatory support. The participants were enrolled between September 2015 and March 2021.

Among patients enrolled in the AVeC Study, 86 patients with moderate or severe MR including perivalvular leakage after mitral valve replacement, without having AS, hypertrophic obstructive cardiomyopathy, or treatment with a left ventricular assist device, were analyzed. We subsequently excluded 2 patients due to missing data. Thus, 84 MR patients were analyzed here. Their clinical data were collected from their clinical records. MR was quantitatively and qualitatively assessed, and severity was defined according to the American College of Cardiology/American Heart Association guidelines based on the results of transthoracic echocardiography [19].

2.2 | Evaluation of VWF-related parameters

For the diagnosis of cardiovascular disease–associated loss of VWF large multimers, so-called VWF multimer analysis has been used as a standard method. The multimers are separated by sodium dodecyl sulfate–containing agarose gel electrophoresis in a nonreducing condition and identified by Western blot analysis using anti-VWF antibody. The VWF large multimer index (VWF-LMI) was calculated as a ratio of the large multimer ratio of the patient's plasma to that of a control's plasma (Siemens Standard plasma) that was analyzed in the adjacent lane (Figure 1) [3,20,21]. We have shown that (1) VWF-LMI was inversely well-correlated with maximal pressure gradient in patients with severe AS [20], (2) loss of VWF large multimers was apparently observed when VWF-LMI was <80% [21], and (3) a rather high rate of patients with severe AS exhibited VWF-LMI < 80% while most of the control patients or patients with peripheral vascular diseases did not show VWF-LMI < 80% [21]. Thus, we have proposed VWF-LMI < 80% as a loss of VWF large multimers [21].

VWF ristocetin co-factor activity (VWF:RCo; BC Von Willebrand Reagent, Siemens Healthcare Diagnostics) and VWF antigen (VWF:Ag; vWF Ag Reagent, Siemens Healthcare Diagnostics) were measured at baseline using the automated coagulation analyzer, CS-5100 (Sysmex) according to the manufacturer's instruction. For patients who underwent surgery or catheter intervention, measurements were also taken on days 1, 2, 7, and 30 up to day 58 after the intervention.

2.3 | Ethics

This study was approved by the ethics committees in all the participating hospitals and research institutes and was registered at University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) (ID: R000019166). It was conducted according to the Declaration of Helsinki by obtaining written informed consent from all patients before enrollment.

2.4 | Statistical analysis

Statistical analysis was performed using SPSS version 18 (International Business Machines Corporation). Continuous data are presented as mean ± SD. Categorical variables are presented as absolute and relative frequencies. Differences in continuous variables between 2 groups were analyzed with the unpaired *t*-test or, if not normally distributed, the Mann–Whitney U-test. Differences in categorical variables were evaluated with the chi-squared test. In a comparison of VWF-LMI between degenerative MR and functional MR, an analysis of covariance was performed. The variables that showed a *P* value of less than .20 in univariate analyses were selected as covariates. Among the patients who underwent surgery or catheter intervention for MR, paired comparisons of VWF parameters or hemoglobin levels between baseline and postprocedural days 1, 2, 7, or 30 were performed using paired *t*-tests. All *P* values are 2-sided. For the overall tests, $P < .05$ was considered significant.

3 | RESULTS

3.1 | Patient characteristics

Baseline characteristics of the analyzed MR patients ($n = 84$) are shown for each etiology of MR in Table 1. The etiology of MR was degenerative in 62 patients (73.8%), functional in 9 patients (10.7%), paravalvular leak

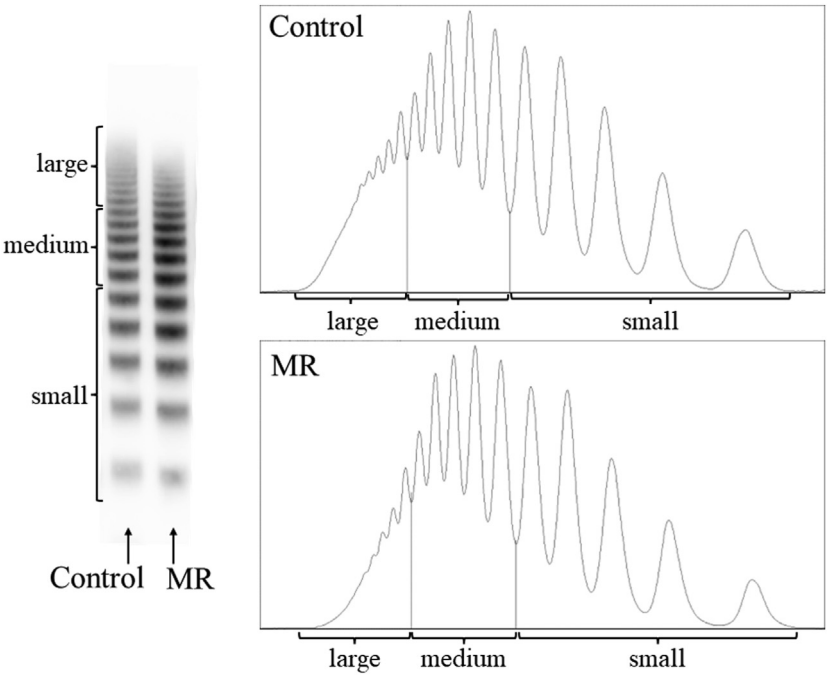

FIGURE 1 The quantification method for von Willebrand factor large multimer index (VWF-LMI). The VWF-LMI is defined as the ratio of von Willebrand factor (VWF) large multimers in a patient compared with that in a control (Siemens Standard plasma). Both samples were analyzed in the same gel under the same conditions in order to decrease interexperimental variability. VWF bands from the lowest to the 5th, from the 6th to the 10th, and higher than the 11th were designated as low, medium, and large multimers, respectively. MR, mitral regurgitation.

$$\text{VWF large multimer ratio} = \frac{\text{Large multimer area}}{\text{Total area}}$$

$$\text{VWF}-\text{LMI (\%)} = \frac{\text{VWF large multimer ratio of the case}}{\text{VWF large multimer ratio of the control}} \times 100$$

after mitral valve replacement in 5 patients (6.0%), and mixed etiology in 8 patients (9.5%). The mean age of patients was 67.8 ± 10.4 years, and 49 patients (58.3%) were male. The major comorbidities were hypertension (47.6%) and atrial fibrillation (39.3%). Atrial fibrillation was especially common in patients with paravalvular leak. The mean left ventricular ejection fraction was 61.9 ± 10.4%. Patients with functional MR showed lower left ventricular ejection fraction than patients with other etiologies. The MR grade was moderate in 25 patients (29.8%) and severe in 59 patients (70.2%).

3.2 | VWF parameters at baseline

While the VWF multimer analysis has not been evaluated by proper quantitative methods, we have proposed its quantitative value that is the VWF-LMI [3,20,21] and it has been getting widely used recently [22,23]. Further, we have proposed a VWF-LMI of 80% as the reasonable reference line of VWF-LMI for the reduction of VWF large multimers [21]. In this study, at baseline, patients with moderate and severe MR had a low VWF-LMI (71.9 ± 22.1%), and 58 patients (69.0%) showed apparent loss of VWF large multimers, which was defined as VWF-LMI < 80%.

While VWF:Ag was relatively high at 142.8 ± 52.3%, VWF:RCo was maintained at a normal level (98.6 ± 43.2%). VWF:RCo/VWF:Ag ratio, which is used for the diagnosis of hereditary von Willebrand disease type 2A when it is <0.7 [24], was also low at 0.69 ± 0.16, and 46 patients (54.8%) showed their VWF:RCo/VWF:Ag ratios < 0.7. VWF:RCo/VWF:Ag ratios were positively correlated with VWF-LMI in MR patients (r_s = 0.418; P < .001; Figure 2A). The receiver operating characteristic curve for VWF-LMI and VWF:RCo/VWF:Ag ratio is shown in Figure 2B. When the VWF:RCo/VWF:Ag ratio of <0.7 was used as a cutoff point, the sensitivity and specificity for the loss of VWF large multimers (VWF-LMI < 80%) were 0.655 and 0.731, respectively (area under the curve, 0.695; 95% CI, 0.569-0.822). The positive predictive value of the VWF:RCo/VWF:Ag ratio of <0.7 for diagnosing the loss of VWF large multimers was 0.844.

Analysis of VWF-LMI in patients with functional MR (n = 9) and degenerative MR (n = 62) revealed that the latter group had lower VWF-LMI (68.9 ± 17.7%) than those with functional MR (89.4 ± 30.5%; P = .005). After adjustment for creatinine, left ventricular ejection fraction, brain natriuretic peptide, and dyslipidemia, MR etiology still had a significant effect on VWF-LMI (Figure 3A). Additionally, analysis of patients with MR due to perivalvular leakage (n = 5) revealed that they also had low VWF-LMI (61.0 ± 36.9%), although there was no significant difference between VWF-LMI of patients with perivalvular leakage and VWF-LMI of patients with degenerative (P = .66) or functional MR (P = .15). A comparison of VWF-LMI between moderate MR and severe MR did not show any difference between the 2 groups (Figure 3B).

TABLE 1 Characteristics of the patients at baseline.

MR etiology	Degenerative MR (*n* = 62)	Functional MR (*n* = 9)	Paravalvular leak (*n* = 5)	Mixed or other (*n* = 8)	Total (*N* = 84)
Age (y)	66.3 ± 10.7	70.8 ± 8.5	71.8 ± 4.8	73.6 ± 9.9	67.8 ± 10.4
Male	38 (61.3)	4 (44.4)	2 (40.0)	5 (62.5)	49 (58.3)
Previous MVP	5 (8.1)	0 (0.0)	0 (0.0)	2 (25.0)	7 (8.3)
Previous MVR	0 (0.0)	0 (0.0)	5 (100.0)	0 (0.0)	5 (6.0)
Hypertension	32 (51.6)	3 (33.3)	1 (20.0)	4 (50.0)	40 (47.6)
Atrial fibrillation	19 (30.6)	5 (55.6)	4 (80.0)	5 (62.5)	33 (39.3)
Diabetes mellitus	7 (11.3)	1 (11.1)	0 (0.0)	2 (25.0)	10 (11.9)
Dyslipidemia	14 (22.6)	0 (0.0)	0 (0.0)	2 (25.0)	16 (19.0)
Oral anticoagulant therapy	14 (22.6)	6 (66.7)	4 (80.0)	5 (62.5)	29 (34.5)
Oral antiplatelet therapy	5 (8.1)	8 (88.9)	1 (20.0)	1 (12.5)	15 (17.9)
History of bleeding	6 (9.7)	1 (11.1)	0 (0.0)	0 (0.0)	7 (8.3)
History of gastrointestinal bleeding	5 (8.1)	1 (11.1)	0 (0.0)	0 (0.0)	6 (7.1)
Positive fecal occult blood	7 (11.3)	2 (22.2)	0 (0.0)	4 (50.0)	13 (15.5)
BARC ≥ 2 bleeding	4 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (4.8)
Endoscopy	14 (22.6)	3 (33.3)	2 (40.0)	4 (50.0)	23 (27.4)
Angiodysplasia	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)
History of intracranial hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine (mg/dL)	1.06 ± 1.41	1.18 ± 0.53	1.43 ± 0.52	1.09 ± 0.31	1.10 ± 1.23
BNP (pg/mL)	95.8 ± 91.2	257.3 ± 340.3	304.8 ± 400.2	137.0 ± 96.0	129.1 ± 172.4
Hemoglobin (g/dL)	13.3 ± 1.4	12.5 ± 3.0	9.8 ± 1.5	12.0 ± 2.2	12.9 ± 1.9
Hemoglobin < 11.0 g/dL	3 (4.8)	2 (22.2)	4 (80.0)	3 (37.5)	12 (14.3)
Platelet ($\times 10^3/\mu L$)	183 ± 49	184 ± 77	134 ± 18	182 ± 54	180 ± 52
Left ventricular ejection fraction (%)	65.1 ± 5.4	48.7 ± 20.1	54.1 ± 12.2	56.1 ± 8.8	61.9 ± 10.4
MR moderate	13 (21.0)	4 (44.4)	5 (100.0)	3 (37.5)	25 (29.8)
MR severe	49 (79.0)	5 (55.6)	0 (0.0)	5 (62.5)	59 (70.2)
AR ≥ moderate	5 (8.1)	1 (11.1)	0 (0.0)	2 (25.0)	8 (9.5)
TR ≥ moderate	14 (22.6)	4 (44.4)	0 (0.0)	2 (25.0)	20 (23.8)
VWF-LMI (%)	68.9 ± 17.7	89.4 ± 30.5	61.0 ± 36.9	82.4 ± 23.6	71.9 ± 22.1
VWF-LMI < 80%	46 (74.2)	4 (44.4)	4 (80.0)	4 (50.0)	58 (69.0)
VWF-LMI < 70%	30 (48.4)	2 (22.2)	3 (60.0)	3 (37.5)	38 (45.2)
VWF-LMI < 60%	15 (24.2)	1 (11.1)	3 (60.0)	2 (25.0)	21 (25.0)
VWF:Ag (%)	136.4 ± 46.6	168.5 ± 84.0	146.9 ± 33.0	161.4 ± 56.3	142.8 ± 52.3
VWF:RCo (%)	92.6 ± 39.7	104.9 ± 38.8	99.7 ± 44.0	137.3 ± 59.6	98.6 ± 43.2
VWF:RCo/VWF:Ag ratio	0.68 ± 0.14	0.67 ± 0.22	0.66 ± 0.18	0.83 ± 0.14	0.69 ± 0.16
Factor VIII (%)	86.1 ± 31.4	71.4 ± 23.1	121.4 ± 24.1	106.9 ± 40.6	88.6 ± 32.6
ADAMTS-13 (%)	57.2 ± 20.7	56.2 ± 24.7	40.2 ± 22.0	67.1 ± 43.4	57.0 ± 24.2

Data are shown as number (%) or mean ± SD.

All participants of this study were Japanese.

ADAMTS-13, a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13; AR, aortic regurgitation; BARC, Bleeding Academic Research Consortium; BNP, B-type natriuretic peptide; MR, mitral regurgitation; MVP, mitral valve plasty; MVR, mitral valve replacement; TR, tricuspid regurgitation; VWF:Ag, von Willebrand factor antigen; VWF-LMI, von Willebrand factor large multimer index; VWF:RCo, von Willebrand factor ristocetin co-factor.

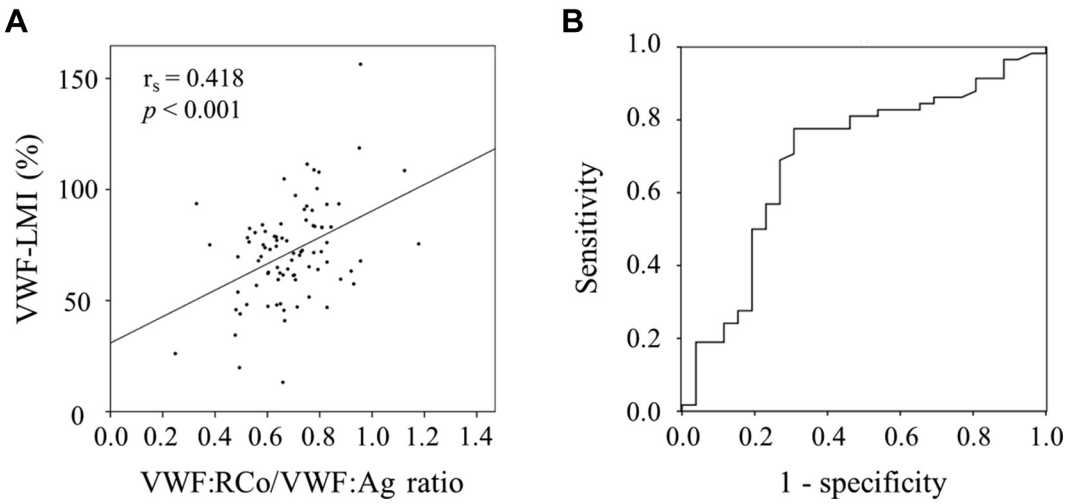

FIGURE 2 (A) Correlation of von Willebrand factor ristocetin co-factor/von Willebrand factor antigen (VWF:RCo/VWF:Ag) with von Willebrand factor large multimer index (VWF-LMI). (B) The receiver operating characteristic curve for VWF:RCo/VWF:Ag for the loss of VWF-LMI (<80.0%). When the VWF:RCo/VWF:Ag of <0.7 was used as a cutoff point, the sensitivity and specificity for the loss of VWF large multimers were 0.655 and 0.731, respectively (area under the curve, 0.695; 95% CI, 0.569-0.822).

3.3 | Periprocedural changes in VWF parameters

Table 2 shows the characteristics and procedural results of 44 patients who underwent mitral valve intervention; 36 patients were treated with mitral valve plasty, 7 patients with mitral valve replacement, and 1 patient with transcatheter mitral valve repair. Except for being slightly younger, their baseline characteristics were not significantly different from those of the total study population. The intervention was successful in 41 patients (93.2%), while postprocedural moderate or severe MR was identified in 1 patient and postprocedural mean mitral valve pressure gradient ≥4 mmHg was identified in 2 patients. The periprocedural transfusion rate was 36.4%. Neither preprocedural nor postprocedural VWF-LMI was associated with the periprocedural transfusion rate. Neither in-hospital bleeding nor in-hospital death was observed.

Figure 4 shows periprocedural changes in VWF parameters. Patients who underwent mitral valve plasty or transcatheter mitral repair and those who underwent mitral valve replacement are shown in separate curves. Mitral valve plasty or transcatheter mitral repair resulted in a postprocedural increase of VWF-LMI, VWF:RCo/VWF:Ag ratio, VWF:Ag, and VWF:RCo. VWF-LMI was increased from 74.5 ± 16.3% to 106.0 ± 23.6% on postprocedural day 1 and remained at 103.0 ± 20.7% on day 7. VWF-LMI slightly decreased to 92.3 ± 22.1% 1 month after the procedure, although it was still significantly higher than baseline VWF-LMI. VWF:RCo/VWF:Ag ratio showed a similar course. VWF:RCo/VWF:Ag ratio increased from 0.71 ± 0.11 to 1.02 ± 0.15 on postprocedural day 1 and remained elevated at 0.91 ± 0.16 on day 7. The VWF:RCo/VWF:Ag ratio slightly decreased to 0.79 ± 0.16 1 month after the procedure but was still significantly higher than the baseline value. VWF:Ag and VWF:RCo showed similar

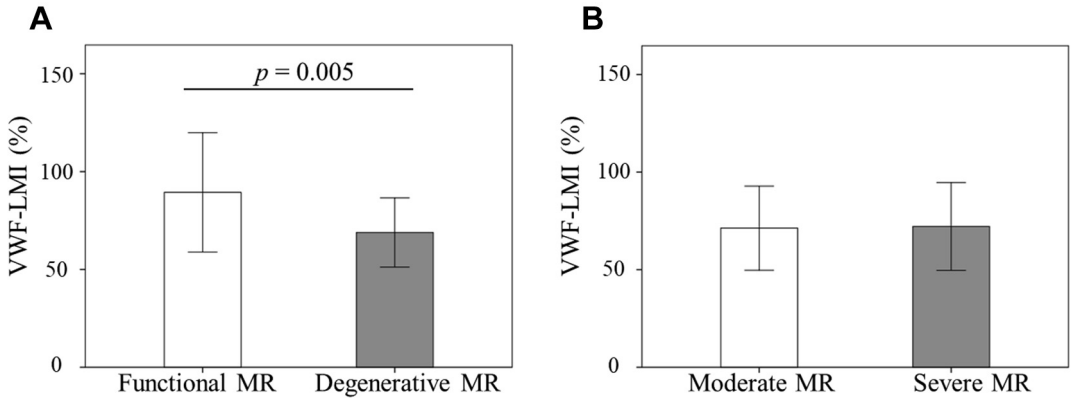

FIGURE 3 (A) Von Willebrand factor large multimer index (VWF-LMI) of patients with functional mitral regurgitation (MR; *n* = 9) and degenerative MR (*n* = 62). (B) VWF-LMI of patients with moderate MR (*n* = 25) and severe MR (*n* = 59). Error bars indicate ±SD.

TABLE 2 Characteristics, procedural results, and periprocedural adverse events of the patients who underwent mitral valve intervention.

Variable	Value
No. of patients	44
Male	27 (61.4)
Hypertension	23 (52.3)
Atrial fibrillation	20 (45.5)
Diabetes mellitus	4 (9.1)
Dyslipidemia	6 (13.6)
Previous MVP	6 (13.6)
Previous MVR	0 (0.0)
MR moderate	8 (18.2)
MR severe	36 (81.8)
MR etiology	
Degenerative MR	38 (86.4)
Functional MR	2 (4.5)
Paravalvular leak	0 (0.0)
Mixed or other	4 (9.1)
Creatinine (mg/dL)	1.08 ± 1.41
BNP (pg/mL)	124.8 ± 124.9
Hemoglobin (g/dL)	13.4 ± 1.4
Hemoglobin < 11.0 g/dL	3 (6.8)
Platelet ($\times 10^3/\mu L$)	18.3 ± 4.3
Left ventricular ejection fraction (%)	63.4 ± 5.7
History of gastrointestinal bleeding	3 (6.8)
Positive fecal occult blood	6 (13.6)
AR ≥ moderate	4 (9.1)
TR ≥ moderate	13 (29.5)
Procedure	
MVP	36 (81.8)
MVR	7 (15.9)
TMVR	1 (2.3)
Postoperative residual MR ≥ moderate	1 (2.3)
Postoperative mean mitral valve gradient ≥ 4 mm Hg	2 (4.5)
Perioperative transfusion	16 (36.4)
In-hospital stroke	1 (2.3)
In-hospital bleeding	0 (0.0)
In-hospital death	0 (0.0)

Data are shown as number (%) or mean ± SD.

AR, aortic regurgitation; BNP, B-type natriuretic peptide; MR, mitral regurgitation; MVP, mitral valve plasty; MVR, mitral valve replacement; TMVR, transcatheter mitral valve repair; TR, tricuspid regurgitation.

changes as well; they increased substantially on postprocedural day 1 and gradually decreased by 1 month but remained significantly higher than the baseline values. VWF parameters after mitral valve replacement showed similar changes, although data from 1 month after the procedure did not show a statistically significant increase compared with preoperative data.

3.4 | Bleedings

The hemoglobin level of 84 MR patients at baseline was 12.9 ± 1.9 g/dL, and 12 patients (14.3%) exhibited hemoglobin levels below 11 g/dL. Seven patients (8.3%) had a history of bleeding within 3 years prior to enrollment, 6 of whom (7.1%) had gastrointestinal bleeding. Of those, 4 patients (4.8%) demonstrated BARC (Bleeding Academic Research Consortium) [25] ≥ 2 bleeding (any overt, actionable sign of hemorrhage) and angiodysplasia was detected in 1 patient. Although the clinical characteristics of those 7 patients were comparable to that of the study population, the ratio of antiplatelet drug use was high (42.9%; Table 3). The 84 MR patients were placed into 2 groups: the high VWF-LMI group (VWF-LMI ≥ 80%; n = 26) and the low VWF-LMI group (VWF-LMI < 80%; n = 58). As shown in Table 4, no baseline characteristics, including bleeding history, were statistically different between the 2 groups. Among patients who underwent surgery or catheter intervention for MR, hemoglobin level 1 month after the procedure (12.1 ± 1.8 g/dL) did not increase but rather decreased significantly from hemoglobin level at baseline (13.4 ± 1.4 g/dL; Figure 5A).

Upper (n = 21) and/or lower (n = 13) gastrointestinal endoscopy was performed in 23 patients (27.4%), including 5 patients with a history of gastrointestinal bleeding, with their hemoglobin level at 11.4 ± 2.9 g/dL. The reasons for undergoing endoscopy were investigation for overt gastrointestinal bleeding in 5 patients, evaluation of positive fecal occult blood test in 11 patients, investigation for anemia in 6 patients, and evaluation of suspicious gastric cancer in 1 patient (Figure 5B). Angiodysplasia was detected in 2 of the 23 patients (8.7%): 1 of the 21 patients (4.8%) who underwent upper gastrointestinal endoscopy and 1 of the 13 patients (7.7%) who underwent lower gastrointestinal endoscopy (Figure 5C). One was an 80-year-old male who had a history of atrial fibrillation and chronic kidney disease with a creatinine level of 1.68 mg/dL and was using oral anticoagulants. He underwent gastrointestinal endoscopies for evaluation of positive fecal blood test, and angiodysplasia in the stomach was detected. His transthoracic echography showed severe degenerative MR and moderate tricuspid regurgitation with an ejection fraction of 74%. His hemoglobin level was 12.3 g/dL, VWF-LMI was 83.0%, VWF:Ag was 289.1%, VWF:RCo was 233.7%, and VWF:RCo/VWF:Ag ratio was 0.81. The other was a 78-year-old female who had a history of hypertension, diabetes mellitus, and chronic kidney disease with a creatinine level of 1.34 mg/dL and was not using oral anticoagulant or antiplatelet due to overt gastrointestinal bleeding. She underwent a lower gastrointestinal endoscopy for investigation of the bleeding, and angiodysplasia in the descending colon was detected. Her transthoracic echography showed moderate degenerative MR and moderate tricuspid regurgitation with an ejection fraction of 66%. Her hemoglobin level was 11.2 g/dL, VWF-LMI was 72.0%, VWF:Ag was 220.8%, VWF:RCo was 178.0%, and VWF:RCo/VWF:Ag ratio was 0.81.

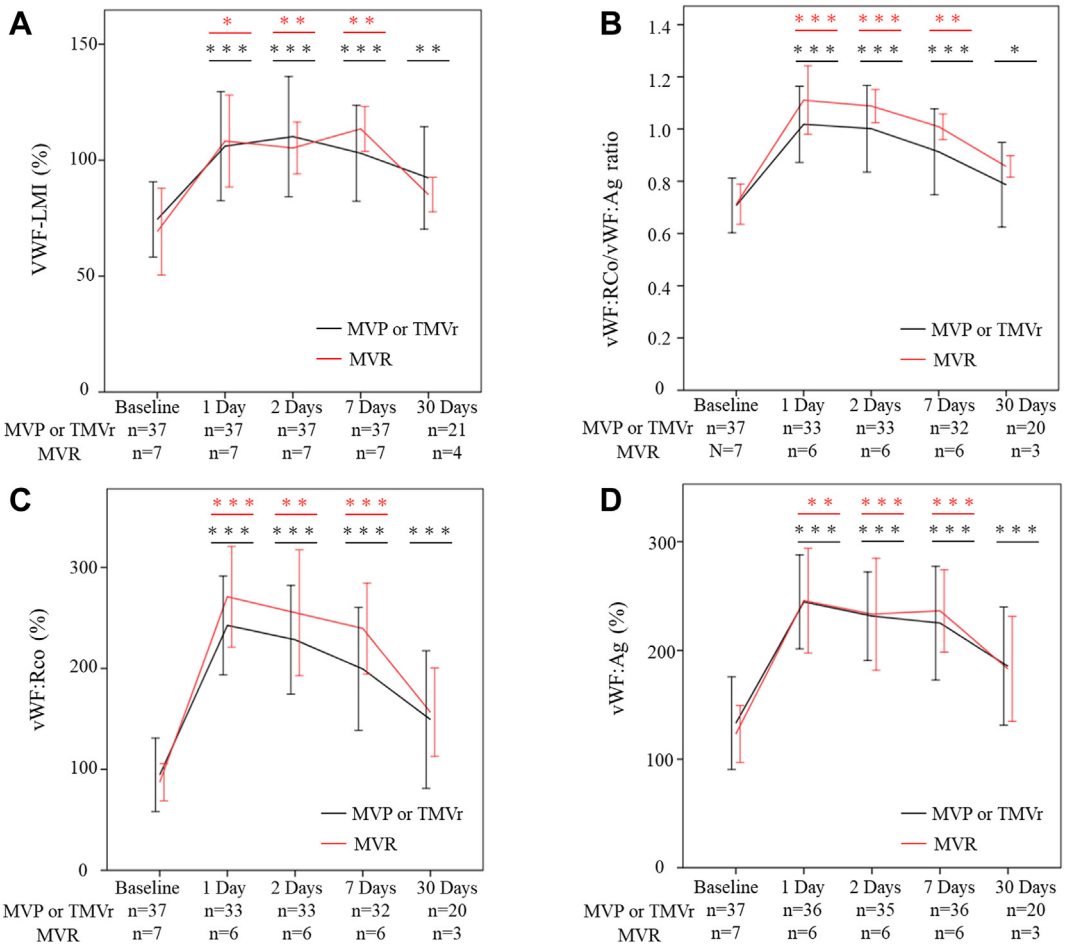

FIGURE 4 Periprocedural changes in von Willebrand factor (VWF) parameters in patients who underwent mitral valve replacement or other procedures (mitral valve plasty or transcatheter mitral valve repair). (A) von Willebrand factor large multimer index (VWF-LMI). (B) von Willebrand factor ristocetin co-factor/von Willebrand factor antigen (VWF:RCo/VWF:Ag) ratio. (C) VWF:RCo. (D) VWF:Ag. $^{*}P < .05$ vs before the procedure. $^{**}P < .01$ vs before the procedure. $^{***}P < .001$ vs before the procedure. Error bars indicate ±SD. MVP, mitral valve plasty; MVR, mitral valve replacement; TMVr, transcatheter mitral valve repair.

4 | DISCUSSION

In this study, we have systematically analyzed 84 patients with moderate or severe MR by focusing on loss of VWF large multimers and gastrointestinal bleeding. It is well known that AS causes the loss of VWF large multimers and gastrointestinal bleeding from angiodysplasia by many studies [5–7]. Therefore, we first dared to compare these incidences and their relationships in MR patients with those in AS patients to evaluate the impact of the loss of VWF large multimers on clinical bleeding in MR patients.

We showed that the VWF-LMI was 71.9 ± 22.1% and hemoglobin level was 12.9 ± 1.9 g/dL, including 12 patients (14.3%) with hemoglobin levels below 11.0 g/dL. We have reported that patients with AS had similar or even higher VWF-LMI (73.2% or 78.2%) and lower hemoglobin levels (9.5 g/dL or 11.4 g/dL) [20,21]. We have also reported that 37.7% of 3403 patients with severe AS showed hemoglobin levels less than or equal to 10.9 g/dL [26]. Thus, compared with patients with AS, patients with MR appear to have rather higher hemoglobin levels despite having similar or even lower VWF-LMI.

We have recently conducted a prospective study, which enrolled patients with hemoglobin levels below 11.0 g/dL and severe AS [27]. All patients underwent examinations of the entire gastrointestinal tract by endoscopy and angiodysplasia was detected in 94% of patients, including 26%, 69%, and 49% in the stomach, small intestine, and colon, respectively. Importantly, 10% of patients exhibited silent active bleeding from gastrointestinal angiodysplasia. With these data, we have speculated that such silent bleeding contributes much to anemia in patients with severe AS. Another previous study showed that 22.5% of patients with severe AS underwent endoscopic examinations in a clinical setting. Of those, 28.8% had angiodysplasia, 13.4% in upper gastrointestinal endoscopy, 71.4% in enteroscopy, and 26.3% in lower gastrointestinal endoscopy [28]. In this current study, 27.4% of MR patients underwent endoscopic examination and only 8.7% of patients had angiodysplasia, including 4.8% and 7.7% of patients in the stomach and colon, respectively. Thus, the frequency of angiodysplasia in MR patients was much lower than in AS patients, which may explain why MR patients had lower frequency of anemia than AS patients despite having similar loss of VWF large multimers.

TABLE 3 Clinical characteristics of patients with a history of bleeding.

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (y)	78	73	69	55	76	69	61
Sex	Female	Female	Male	Male	Male	Male	Male
Description of bleeding	GI bleeding (suspected from angiodysplasia)	Gum bleeding	Bleeding from gastric cancer	GI bleeding of unknown origin	Bleeding from gastric ulcer	Bleeding from gastric ulcer and xanthoma	Bleeding from colon polyps
BARC ≥ 2 bleeding	Yes	No	No	Yes	Yes	Yes	No
Endoscopy	Yes	No	Yes	Yes	No	Yes	Yes
Angiodysplasia	Yes	No	No	No	No	No	No
OAC use	No	Yes	Yes	No	No	No	No
Antiplatelet use	No	No	Yes	Yes	Yes	No	No
MR etiology	Degenerative	Degenerative	Functional	Degenerative	Degenerative	Degenerative	Degenerative
MR grade	Moderate	Moderate	Severe	Severe	Severe	Severe	Severe
Hemoglobin (g/dL)	11.2	12	12.7	11.4	14.3	11.9	14.2
VWF-LMI (%)	72	78.6	93.6	13.2	75.5	76.4	80.6
VWF:Ag (%)	220.8	139.4	84.7	223.9	54.6	69.1	86.5
VWF:RCo (%)	178.0	88.4	27.9	147.6	64.3	36.1	47.8
VWF:RCo/VWF:Ag ratio	0.81	0.63	0.33	0.66	1.18	0.53	0.55

BARC, Bleeding Academic Research Consortium; GI, gastrointestinal; MR, mitral regurgitation; OAC, oral anticoagulant; VWF:Ag, von Willebrand factor antigen; VWF-LMI, von Willebrand factor large multimer index; VWF:RCo, von Willebrand factor ristocetin co-factor.

TABLE 4 Comparison of clinical data between high and low von Willebrand factor large multimer index groups.

Variable	VWF-LMI ≥ 80 (*n* = 26)	VWF-LMI < 80 (*n* = 58)	*P* value
Age (y)	67.4 ± 11.7	67.9 ± 9.8	.84
Male	13 (50.0)	36 (62.1)	.34
Hypertension	13 (50.0)	27 (46.6)	.82
Atrial fibrillation	9 (34.6)	24 (41.4)	.63
Diabetes mellitus	4 (15.4)	6 (10.3)	.49
Dyslipidemia	5 (19.2)	11 (19.0)	1.00
Previous MVP	3 (11.5)	4 (6.9)	0.67
Previous MVR	1 (3.8)	4 (6.9)	1.00
MR moderate	7 (26.9)	18 (31.0)	.80
MR severe	19 (73.1)	40 (69.0)	.80
MR etiology			
Degenerative mitral regurgitation	16 (61.5)	46 (79.3)	.11
Functional mitral regurgitation	5 (19.2)	4 (6.9)	.13
Paravalvular leak	1 (3.8)	4 (6.9)	1.00
Mixed or other	4 (15.4)	4 (6.9)	.25
Creatinine (mg/dL)	0.98 ± 0.46	1.15 ± 1.45	.57
BNP (pg/mL)	145.0 ± 207.6	121.9 ± 155.8	.60
Hemoglobin (g/dL)	12.6 ± 2.0	13.0 ± 1.9	.43
Hemoglobin < 11.0 g/dL	4 (15.4)	8 (13.8)	1.00
Platelet (× 10^3/μL)	194 ± 53	173 ± 51	.09
Left ventricular ejection fraction (%)	58.9 ± 13.8	63.2 ± 8.3	.15
History of gastrointestinal bleeding	2 (7.7)	4 (6.9)	1.00
Positive fecal occult blood	5 (19.2)	8 (13.8)	.53
AR ≥ moderate	2 (7.7)	6 (10.3)	1.00
TR ≥ moderate	7 (26.9)	13 (22.4)	.78

Data are shown as number (%) or mean ± SD.

AR, aortic regurgitation; BNP, B-type natriuretic peptide; MR, mitral regurgitation; MVP, mitral valve plasty; MVR, mitral valve replacement; TR, tricuspid regurgitation; VWF-LMI, von Willebrand factor large multimer index.

In patients with Heyde syndrome, the bleeding is thought to be attributed to loss of VWF large multimers and angiodysplasia. While the exact pathogenesis of angiodysplasia remains unclear, loss of VWF large multimers *per se* and/or hemodynamic factors including impaired mucosal blood perfusion due to decreased cardiac output, reduced pulse pressure, and/or chronic hypoxia in mucosa of the gastrointestinal tract are proposed to be the causes [8]. Compared with AS, MR is considered to cause preserved blood perfusion due to the maintenance of blood pressure and pulse pressure, although it causes a similar degree of loss of VWF large multimers. Our data indicate that angiodysplasia can be developed but is less common in MR patients, which suggests that hemodynamic factors contribute more to the development of angiodysplasia than the loss of VWF large multimers itself. Differences in characteristics between MR patients and AS patients such as age or anticoagulant usage rate can influence the frequency of bleeding. Additionally, it is proposed that aging can lead to the development of angiodysplasia through chronic obstruction of submucosal veins [29]. Taking these differences into account, our data still can suggest that the loss of VWF large multimers alone is not enough to cause angiodysplasia. Furthermore, our results showed that the hemoglobin level 1 month after mitral valve intervention (12.1 ± 1.8 g/dL) was rather lower than the hemoglobin level before the interventions (13.4 ± 1.4 g/dL). Surgical invasion and higher frequencies of antithrombotic therapy may contribute to the decrease. The fact that hemoglobin level reportedly improved after aortic valve replacement for AS [20] but not after mitral valve intervention in our results also supports our hypothesis that the hemodynamic effects of AS may contribute more to the development of angiodysplasia rather than loss of VWF large multimers.

VWF:RCo/VWF:Ag ratio is widely used for the diagnosis of hereditary von Willebrand disease type 2A and can be measured with an automated coagulation analyzer in clinical laboratories [24]. However, the diagnostic value of VWF:RCo/VWF:Ag ratio for the loss of VWF large multimers in MR patients has not usually been evaluated. This current study revealed a moderate positive correlation between VWF:RCo/VWF:Ag ratio and VWF-LMI in MR patients. Even though the sensitivity and specificity were not so high (0.655 and 0.731, respectively), VWF:RCo/VWF:Ag could be useful for the evaluation of VWF large multimers associated with MR to some extent, considering that measuring VWF:RCo/VWF:Ag ratio is easier than VWF multimer analysis and that this current study revealed the positive predictive value of as high as 0.844.

Native mitral valvular regurgitation is classified as degenerative or functional. It was previously reported that degenerative MR was associated with lower VWF activity than functional MR as evaluated by VWF activity/antigen ratios [13]. The result of our study was consistent with that report. Higher shear stress generated by the eccentric jet morphology of degenerative MR than that of functional MR is a possible explanation. Although lower left ventricular ejection fraction in patients with functional MR can cause lower shear stress, left ventricular ejection fraction did not show a correlation with VWF-LMI (data not shown) and the etiology of MR still demonstrated a significant impact on VWF-LMI even after adjustment for covariates, including left ventricular ejection fraction. While it has been reported that the loss of VWF large multimers was predictive of the presence of aortic regurgitation after transcatheter aortic valve replacement [30], reports about the association of loss of VWF large multimers with perivalvular leakage after mitral valve replacement are limited to a case series [31]. In our study, 5 patients with perivalvular leakage showed lower VWF-LMI (61.0 ± 36.9%) compared with MR of other causes, although that was not statistically significant possibly due to the small sample size.

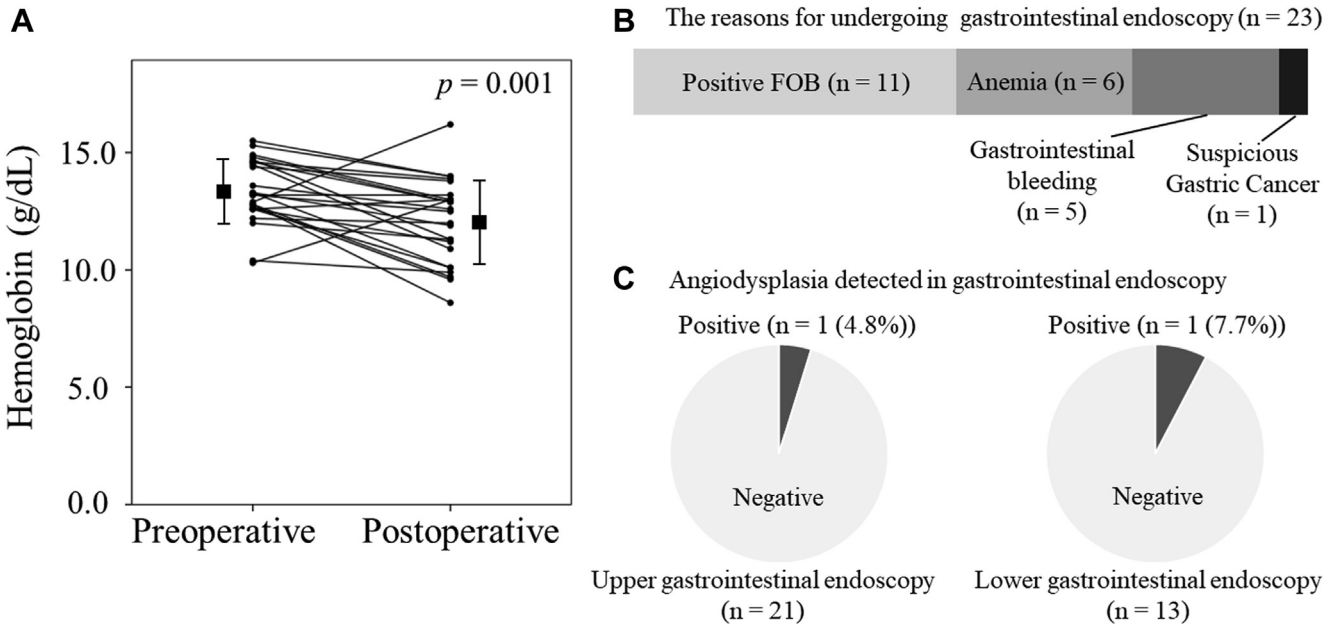

FIGURE 5 (A) Changes in hemoglobin levels among patients who had mitral valve intervention (n = 25). Squares represent the mean hemoglobin levels, and the corresponding vertical lines represent the SD. (B) The reasons for undergoing gastrointestinal endoscopy. (C) The ratios of patients with angiodysplasia detected in gastrointestinal endoscopy. FOB, fecal occult blood.

In this study, we showed that VWF-LMI and the VWF:RCo/VWF:Ag ratio significantly increased on postprocedural days 1, 2, and 7, which was maintained 1 month after mitral plasty or transcatheter mitral repair. VWF parameters also increased after mitral valve replacement, although, at 1 month after the procedure, the parameters were not significantly higher than preoperatively possibly due to a small sample size. The increase in VWF parameters on postprocedural days 1 and 2 could be partly due to the increased secretion of VWF from endothelial cells in response to the treatment procedure in addition to the disappearance of high shear stress [3,32]. The increase of VWF parameters 1 month after the procedure could be purely due to the disappearance of high shear stress by the treatment of MR. Contrary to our results, Meindl et al. [13] reported that transcatheter mitral valve repair did not improve VWF activity/VWF:Ag ratios 4 weeks after the procedure. It has been reported that, compared with patients who received mitral valve plasty or mitral valve replacement, patients treated with transcatheter mitral valve repair had greater residual MR and higher postprocedural mitral valve gradient [33,34]. Both factors could prevent postprocedural reduction of shear stress. Since most of the patients in our study underwent mitral valve plasty or mitral valve replacement, it is assumed that the improvement of large VWF multimers is influenced by the type of procedure and that mitral valve plasty or mitral valve replacement is more effective than transcatheter mitral valve repair for it.

This study has some limitations. First, the endoscopic examinations were not systematically performed. Therefore, we might have underestimated the prevalence of patients with angiodysplasia. Second, the number of patients analyzed in this study was not large. Thus, the numbers of patients with functional MR, perivalvular leakage, and patients who underwent transcatheter mitral valve repair were small. Further studies with a larger number of patients are needed to clarify the characteristics of loss of VWF large multimers associated with MR more precisely.

In conclusion, this multicenter prospective study showed that (1) loss of VWF large multimers was common in MR patients, comparable in patients with severe AS, and each MR etiology had a different impact on the loss of VWF large multimers, (2) the loss of VWF large multimers in patients with MR improved rapidly after mitral valve intervention, and the improvement was maintained for at least 1 month, and (3) the rate of MR patients having anemia was far less compared with that of AS patients, which could be due to having less angiodysplasia.

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AUTHOR CONTRIBUTIONS

H. Takiguchi, M. Miura, and H.H. (the Coordinator of the AVeC [acquired von Willebrand syndrome co-existing with cardiovascular diseases] Study) designed the study, interpreted the data, and wrote the draft of the manuscript. H. Takiguchi, M. Miura, S. Shirai, Yoshimitsu Soga, M. Hanyu, G.S., Yoshiharu Soga, Y.A., S.W., T.K., H. Takahama, S.Y., T.N., Y.F., N.Y., H.S., K.S., Y. Saiki, K. Kaikita, K.T., and T.T. contributed to the patient enrollment for the study. T.D., M.Y., M.S., Y.E., K. Kokame, M. Hayakawa, M. Matsumoto, N.i.O., S. Sugawara, S.F., and Y.K. performed hematological analysis. All authors contributed to the literature review, final draft writing, and critical revision. All authors approved the final version of the paper.

RELATIONSHIP DISCLOSURE

Some of the results were obtained as collaborative work with Sysmex Corporation. Y.K. is an employee of Sysmex Corporation. Dr Takiguchi has been an employee of Eli Lilly Japan since April 1, 2024. All other authors declare they have no conflicts of interest to disclose.

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