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Increased von Willebrand Factor to ADAMTS13 Ratio as a Predictor of Thrombotic Complications Following a Major Hepatectomy

Shin-ichiro Kobayashi, MD; Yukihiro Yokoyama, MD; Tadashi Matsushita, MD; Motoshi Kainuma, MD; Tomoki Ebata, MD; Tsuyoshi Igami, MD; Gen Sugawara, MD; Yu Takahashi, MD; Masato Nagino, MD

Objective: To investigate the association between changes in procoagulant/fibrinolytic factors and thrombotic complications following a major hepatectomy. Little information is available regarding the changes in procoagulant/fibrinolytic factors (such as the von Willebrand factor [vWF] and a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13 [ADAMTS13]), following a major hepatectomy.

Design: Patients who underwent a major hepatectomy from 2010 to 2011 were enrolled. Patients who underwent a pancreatoduodenectomy (PD) during the same period were also observed as controls, for whom operation time and amount of intraoperative blood loss were comparable to those of the patients who underwent a major hepatectomy. Blood samples were prospectively collected to measure various procoagulant/fibrinolytic factors, including vWF and ADAMTS13.

Setting: Nagoya University Hospital, Japan.

Patients: A total of 50 patients who underwent a major hepatectomy and a total of 23 patients who underwent a PD.

Results: The levels of vWF in the patients who underwent a major hepatectomy increased from before the operation to the seventh postoperative day and were significantly higher than those observed in the patients who underwent a PD. The ADAMTS13 activity in the patients who underwent a major hepatectomy gradually decreased throughout the first 14 postoperative days. In contrast, ADAMTS13 activity in the patients who underwent a PD returned to nearly normal levels within 2 weeks. Three patients who underwent a major hepatectomy had clinically significant thrombotic complications within the first 2 weeks after surgery; however, none of the patients who underwent a PD had thrombotic complications. The vWF to ADAMTS13 ratios of the 3 patients who experienced thrombotic complications were extremely high even before the occurrence of complications. No other procoagulant/fibrinolytic factors showed a marked association with thrombotic events. The vWF to ADAMTS13 ratio was significantly correlated with the estimated liver remnant volume ($P < .001$) but not with other preoperative or intraoperative factors.

Conclusions: The vWF to ADAMTS13 ratio may be a potentially useful marker in predicting thrombotic complications following a major hepatectomy.

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Author Affiliations: Division of Surgical Oncology, Department of Surgery (Drs Kobayashi, Yokoyama, Ebata, Igami, Sugawara, Takahashi, and Nagino), Department of Anesthesiology, Nagoya University Graduate School of Medicine (Dr Kainuma), and Department of Transfusion Medicine, Nagoya University Hospital (Dr Matsushita), Japan.

THROMBOTIC COMPLICATIONS following major surgery are one of the most devastating events leading to postoperative mortality.[1,2] They can be induced by venous stasis, hypercoagulable states, and endothelial injuries, as stated in Virchow's triads.[3]

See Invited Critique at end of article

During hepatobiliary surgery, massive bleeding, repetitive clamping of hepatoduodenal ligaments, resections and reconstructions of major vessels, and major reductions in liver volume can trigger the development of thrombotic complications. However, predicting thrombotic complications is difficult by conventional blood testing for procoagulant/fibrinolytic factors.

The von Willebrand factor (VWF) is a large multimeric glycoprotein that is essential for platelet adhesion and thrombus formation.[4] The vWF subunits are synthesized in endothelial cells and subsequently assemble into large multimers that are secreted during vascular injury.[5-7] A disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13 (ADAMTS13) is a metalloprotease produced primarily by hepatic stellate cells.[8,9] Unusually large vWF multimers induce vWF-mediated platelet aggregation,

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Table 1. Clinical Characteristics of the Patients Who Underwent a Major Hepatectomy or a Pancreatoduodenectomy

Characteristic	No. of Patients: Major Hepatectomy (n = 50)	No. of Patients: Pancreatoduodenectomy (n = 23)	*P* Value
Sex			
Male	33	13	.45
Female	17	10	
Age, mean (SD), y	66 (10)	63 (9)	.27
Disease			
CC	44	3	
GBC	3	1	
Benign	1	1	
HCC	2	0	
PC	0	11	
VC	0	4	
IPMN	0	3	
Comorbid illness, No. (%)			
Diabetes mellitus	3 (6.0)	5 (21.7)	.10
Hepatitis	2 (4.0)	1 (4.3)	>.99
Liver cirrhosis	0 (0)	0 (0)	
Preoperative cholangitis, No. (%)	6 (12.0)	5 (21.7)	.31
Obstructive jaundice, No. (%)	29 (58.0)	13 (56.5)	>.99
Preoperative biliary drainage, No. (%)			
PTBD	6	0	
ENBD	34	10	
EBS	0	4	
Metallic stent	1	0	
No drainage	9	9	

Abbreviations: CC, cholangiocarcinoma; EBS, endoscopic biliary stenting; ENBD, endoscopic nasobiliary drainage; GBC, gallbladder carcinoma; HCC, hepatocellular carcinoma; IPMN, intraductal papillary mucinous neoplasma; PC, pancreas cancer; PTBD, percutaneous transhepatic biliary drainage; VC, carcinoma of the ampulla of Vater.

which results in the development of thrombotic thrombocytopenic purpura. The ADAMTS13 cleaves unusually large vWF multimers into smaller, less active forms and prevents the formation of thrombi.[10] Therefore, maintaining a balance between the levels of vWF and ADAMTS13 appears to be crucial in preserving microcirculation and macrocirculation, especially under stressful conditions.[11]

Recently, increases in the vWF to ADAMTS13 ratio have been shown to be useful in predicting acute myocardial infarctions,[12] cerebral infarctions,[13] and thrombotic microangiopathies.[14,15] It has been hypothesized that increased vWF to ADAMTS13 ratios may lead to enhanced thrombogenesis. Increased production of vWF has been observed under conditions of endothelial damage,[5] and decreased ADAMTS13 activity has been shown in thrombotic thrombocytopenic purpura,[16] connective tissue diseases,[17] liver diseases,[18] and metastasizing tumors.[19] However, little information is available regarding the alterations in vWF and ADAMTS13 after a major hepatectomy.[20]

In our study, we prospectively collected blood samples and measured the levels of vWF, ADAMTS13, and other procoagulant/fibrinolytic factors in patients who underwent a major hepatectomy. Samples were also collected from patients who underwent a pancreatoduodenectomy (PD) as a control group, in which operation time and amount of intraoperative blood loss were comparable to those from patients who underwent a major hepatectomy. The associations between postoperative thrombotic complications and the levels of vWF, ADAMTS13, and other procoagulant/fibrinolytic factors were also analyzed.

METHODS

PATIENTS

In Nagoya University Hospital in Japan between June 2010 and March 2011, a total of 50 patients who underwent a major hepatectomy and a total of 23 patients who underwent a PD were enrolled in our study. Major hepatectomies included right hepatectomies, left hepatectomies, right trisectionectomies, and left trisectionectomies. Patients with partial resections of the liver, in which an accurate estimation of remnant liver volume was difficult, were excluded. Patients who received scheduled anticoagulant therapy during the perioperative period were also excluded. Written informed consent, which was approved by the human research review committee of the Nagoya University Hospital, was obtained from each patient prior to enrollment in our study (registered University hospital Medical Information Network, http://www.umin.ac.jp/ [umin.ac.jp/ctr Identifier: UMIN000006642]).

The clinical characteristics of the patients who underwent a major hepatectomy or a PD are described in **Table 1**. There were no significant differences in the sex distribution, age, or the incidence of preoperative comorbid illnesses or cholangitis between patients who underwent a major hepatectomy and patients who underwent a PD.

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PERIOPERATIVE MANAGEMENT

Patients with obstructive jaundice underwent endoscopic nasobiliary drainage, percutaneous transhepatic biliary drainage, endoscopic biliary stenting, and/or metallic stenting (Table 1). All bile drained externally from the biliary drainage catheter was replaced orally or via a nasoduodenal tube to maintain intestinal integrity[21] and to help vitamin K insorption to prevent coagulopathy. Because of these treatments, the preoperative levels of procoagulant/fibrinolytic factors were normal in all patients. In general, operations were performed after the total serum bilirubin levels had been normalized in patients who underwent a major hepatectomy and patients who underwent a PD.

Portal vein embolization was indicated when a patient's future liver remnant volume was estimated to be less than 40%. In these cases, the portal vein embolization was performed 2 to 3 weeks prior to the scheduled liver resection (**Table 2**). A portal vein embolization was performed for patients who were scheduled to undergo a right hepatectomy, a right trisectionectomy, or a left trisectionectomy, but it was not performed for any patients scheduled to undergo a left hepatectomy. All portal vein embolizations were performed using the percutaneous transhepatic ipsilateral approach.[22,23] For patients who were scheduled to undergo a major hepatectomy or a PD, autologous blood samples (400-800 mL) were collected 1 to 3 weeks prior to surgery, unless their hemoglobin levels were less than 11 g/dL (to convert to grams per liter, multiply by 10.0).

BLOOD SAMPLING AND MEASUREMENT OF PROCOAGULANT/FIBRINOLYTIC FACTORS

Blood samples were obtained for analysis at the following time points: preoperation, postresection (immediately following tumor resection and prior to digestive reconstruction), postoperation (immediately following surgery), and on the first, second, fourth, seventh, and 14th postoperative days. We measured the levels of ADAMTS13 activity, vWF antigen, coagulation factor VII, fibrinogen, the thrombin-antithrombin III complex, and the plasmin-α2 plasmin inhibitor complex. In addition, we determined the platelet count, the prothrombin time, and the activated partial thromboplastin time.

The level of ADAMTS13 activity was measured using the ADAMTS13 Activity ELISA Kit (Kainos Laboratories, Inc). In this assay, the specific monoclonal antibody, N10, captures ADAMTS13-cleaved vWF fragments, and ADAMTS13 activity is expressed as a percentage of the healthy control value. Plasma vWF antigen levels were measured using an immunoturbidimetric assay (STA-Liatest VWF:Ag; Roche) according to the manufacturer's instructions.

Plasma prothrombin time was measured using the clotting method (STA-Neoplastine Cl; Roche). Factor VII activity was measured using a 1-stage clotting assay with an automated coagulation analyzer (ACL-TOP; Instrumentation Laboratory, Inc). Fibrinogen levels were measured using the clotting method (STA-Fibrinogen; Roche). Activated partial thromboplastin time was also measured using the clotting method (STA-PTT Automate; Roche). Thrombin-antithrombin III complex levels were measured by enzyme immunoassay (Emax microplate; Molecular Devices, Inc), and plasmin-α2 plasmin inhibitor complex levels were measured using a latex photometric immunoassay (LPIA-ACE PPI II; Mitsubishi Chemical Medicine Corp).

STATISTICAL ANALYSIS

Statistical analyses were performed using Dr.SPSS II for Windows version 19.0.1J (SPSS Inc). Quantitative data are expressed as means with standard deviations. The *t* test was used to compare parametric data. Qualitative data were compared using the Pearson χ^2 test or the Fisher exact test, as appropriate. The correlation between the 2 groups, in which the data points were distribution-free, was analyzed using the Spearman correlation coefficient. *P* values of less than .05 were considered to be statistically significant.

Table 2. Major Hepatectomy Data

Variable	Patients (n = 50)
Preoperative portal vein embolization, No. (%)	30 (60.0)
ICG retention rate at 15 min, mean (SD), %	8.9 (5.0)
Plasma disappearance rate of ICG, mean (SD)	0.166 (0.037)
Remnant liver volume, mean (SD), cm^3	540 (170)
Type of hepatectomy, No.	
Left hepatectomy	13
Left hepatectomy with PD	1
Left trisectionectomy	9
Right hepatectomy	11
Right hepatectomy with PD	9
Right trisectionectomy	6
Right trisectionectomy with PD	1
Combined vascular resection, No. (%) of patients with HX	19 (38.0)
Portal vein	18 (36.0)
Hepatic artery	8 (16.0)
Inferior vena cava	1 (2.0)

Abbreviations: HX, major hepatectomy; ICG, indocyanine green retention; PD, pancreatoduodenectomy.

RESULTS

BACKGROUND OF MAJOR HEPATECTOMY

After a portal vein embolization, the mean (SD) indocyanine green (ICG) retention rate at 15 minutes was 8.9% (5.0%), and the mean (SD) plasma disappearance rate of ICG was 0.166 (0.037). The estimated mean (SD) remnant liver volume in patients who underwent a major hepatectomy was 540 (170) mL (Table 2).

The types of hepatectomy performed are summarized in Table 2. For all patients, except for one who underwent a right hepatectomy for hepatocellular carcinoma, en bloc resections of the caudate lobe and extrahepatic bile duct were performed. For 1 patient who underwent a left hepatectomy, 9 patients who underwent a right hepatectomy, and 1 patient who underwent a right trisectionectomy, a PD was combined with a hepatectomy, primarily owing to the longitudinal extension of the cancer to the lower bile duct. The various types of combined vascular resection are also shown in Table 2. In general, intraoperative or postoperative anticoagulant therapy was not routinely performed for any of the study patients unless a clinically significant thrombotic complication was observed.[24]

INTRAOPERATIVE AND POSTOPERATIVE VARIABLES

The mean operation times and the mean amounts of blood loss were not significantly different between patients who

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Table 3. Intraoperative and Postoperative Variables of Major Hepatectomy and Pancreatoduodenectomy

Variable	Patients, No. (%)		P Value
	Major Hepatectomy (n = 50)	Pancreatoduodenectomy (n = 23)	
Operation time, mean (SD), min	593 (136)	567 (186)	.50
Amount of intraoperative blood loss, mean (SD), mL	1756 (1573)	1491 (1724)	.52
Type of transfusion			
Any transfusion	45 (90.0)	17 (73.9)	.09
Autologous	24 (48.0)	12 (52.2)	
Packed red blood cells	17 (34.0)	5 (21.7)	
Fresh frozen plasma	17 (34.0)	3 (13.0)	
Platelet concentrate	3 (6.0)	1 (4.3)	
Fibrinogen	3 (6.0)	1 (4.3)	
Any complications	39 (78.0)	18 (78.3)	.10
Clavien-Dindo classification			
Grade I	12 (24.0)	4 (17.4)	
Grade II	6 (12.0)	4 (17.4)	
Grade IIIa	20 (40.0)	10 (43.5)	
Grade IIIb	0 (0)	0 (0)	
Grade IVa	0 (0)	0 (0)	
Grade IVb	0 (0)	0 (0)	
Grade V[a]	1 (2.0)	0 (0)	
Postoperative hospital stay, mean (SD), d	35 (22)	40 (22)	.39

[a] Mortality.

underwent a major hepatectomy and patients who underwent a PD (**Table 3**). Autologous blood transfusions were performed for 24 of 50 patients (48.0%) who underwent a major hepatectomy and 12 of 23 patients (52.2%) who underwent a PD. There were no significant differences between these 2 groups in the percentage of patients receiving blood transfusions of packed red blood cells, fresh frozen plasma, platelet concentrate, or fibrinogen (Table 3). Also, both the incidences of postoperative complications and the mean lengths of postoperative hospital stay were not significantly different between these 2 groups of patients.

COAGULATION FACTOR VII, FIBRINOGEN, THROMBIN-ANTITHROMBIN III COMPLEX, PLASMIN-α2 PLASMIN INHIBITOR COMPLEX, PLATELET COUNT, PROTHROMBIN TIME, AND ACTIVATED PARTIAL THROMBOPLASTIN TIME

Prior to surgery, there were no significant differences in the levels of any of the examined procoagulant/fibrinolytic factors between patients who underwent a major hepatectomy and patients who underwent a PD (**Figure 1**). However, during the 2 weeks following surgery, the mean prothrombin time and the mean levels of factor VII and fibrinogen were significantly lower in patients who underwent a major hepatectomy than in patients who underwent a PD (Figure 1A, B, and C). The mean activated partial thromboplastin time was significantly lower in patients who underwent a major hepatectomy than in patients who underwent a PD, but only after resection and immediately after the operation (Figure 1D). The mean platelet counts were largely similar between the 2 groups of patients and were within normal levels until postoperative day 4; however, on postoperative days 7 and 14, the mean platelet counts were significantly higher in patients who underwent a PD than in patients who underwent a major hepatectomy (Figure 1E). Over the entire postoperative period examined, the mean levels of thrombin-antithrombin III complex and plasmin-α2 plasmin inhibitor complex were significantly higher in patients who underwent a major hepatectomy than in patients who underwent a PD, which indicates that patients were in a more hypercoagulable and hyperfibrinolytic state after a major hepatectomy than after a PD (Figure 1F and G).

LEVELS of vWF AND ADAMTS13 ACTIVITY

The overall trends in the levels of vWF antigen were similar after a major hepatectomy and after a PD (**Figure 2**). The levels of vWF antigen were significantly higher in patients who underwent a major hepatectomy, even preoperatively. It is noteworthy, however, that the increase of vWF antigen levels in patients who underwent a major hepatectomy was greater than that observed in patients who underwent a PD during the postoperative course (Figure 2A). The vWF antigen levels gradually increased in patients who underwent a major hepatectomy beginning on postoperative day 1, until they reached their highest levels (300%-350%) on postoperative day 4 or 7.

Prior to a hepatectomy, the mean (SD) ADAMTS13 activity in patients who underwent a major hepatectomy was 68% (15%), which was slightly below normal (Figure 2B). The mean (SD) ADAMTS13 activity markedly decreased after surgery (down to 41% [14%] immediately after surgery) and continued to decrease throughout the first 2 postoperative weeks. Even on postoperative day 14, the mean (SD) ADAMTS13 activity was as low as 35% (16%). In sharp contrast, the mean (SD) level of ADAMTS13 activity in patients who underwent a PD was only reduced to 52% (16%) following surgery and began to recover starting on post-

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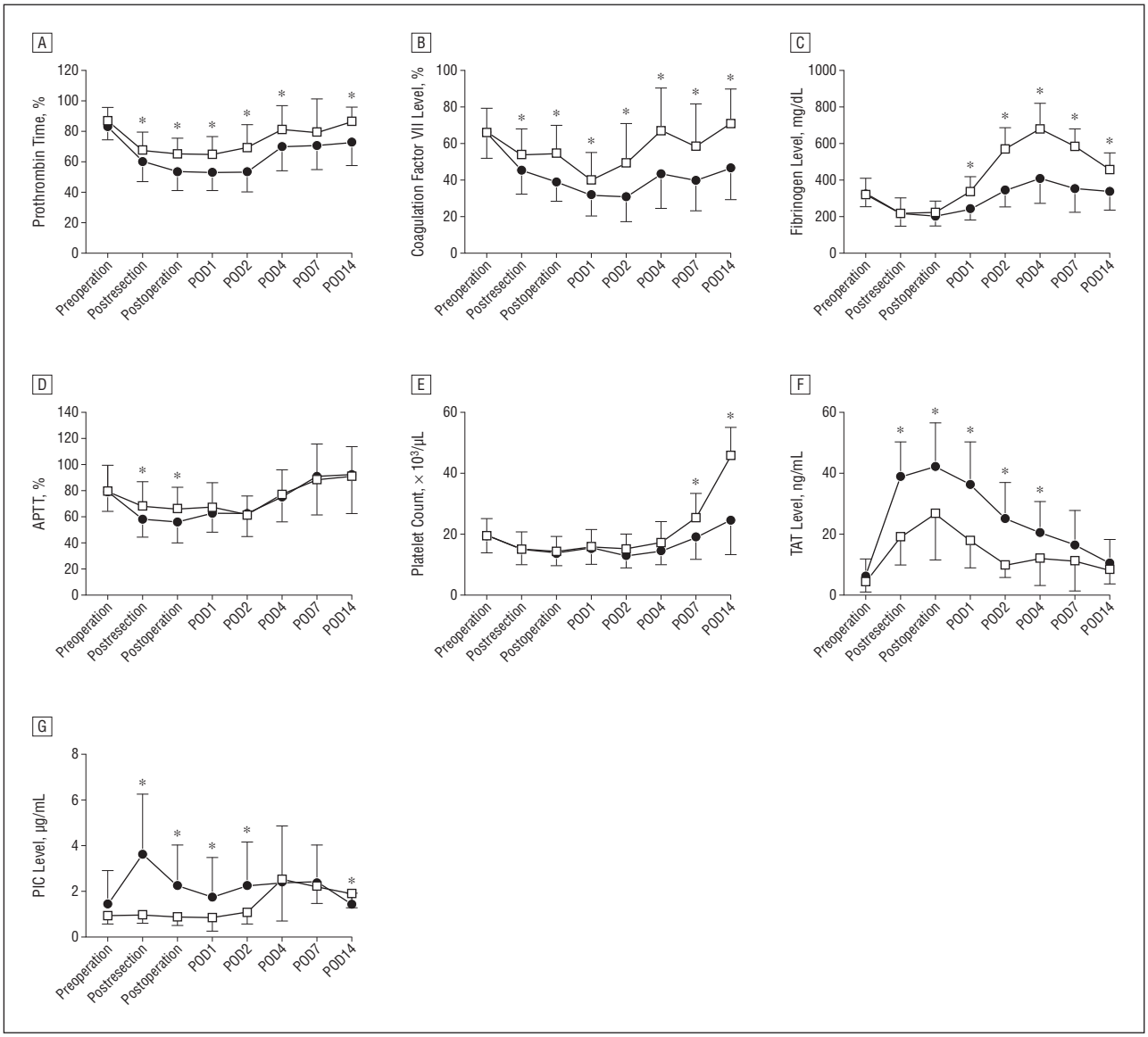

Figure 1. Changes in procoagulant and fibrinolytic factors (A-G) in patients before and after a major hepatectomy (filled circles) or a pancreatoduodenectomy (open squares). Values are expressed as mean values. Error bars indicate SD. $*P < .05$. APTT indicates activated partial thromboplastin time; PIC, plasmin-α2 plasmin inhibitor complex; POD, postoperative day; PT, prothrombin time; TAT, thrombin-antithrombin III complex.

operative day 1. By postoperative day 14, the mean (SD) level of ADAMTS13 activity had recovered to nearly its preoperation level (73% [16%]) (Figure 2B).

Although the mean (SD) vWF to ADAMTS13 ratio in patients who underwent a PD was relatively stable and remained close to normal throughout the 2 postoperative weeks, this ratio was markedly higher in patients who underwent a major hepatectomy, exhibiting a maximum mean (SD) value of 12.5 (5.5) on postoperative day 7. This ratio remained at an abnormally high level until postoperative day 14 (Figure 2C).

Of the 50 patients who had a major hepatectomy, 11 underwent a hepatopancreatoduodenectomy. The mean values of vWF level, ADAMTS13 activity, and VWF to ADAMTS13 ratio between the 39 patients who underwent a hepatectomy and the 11 patients who underwent a hepatopancreatoduodenectomy were compared. The mean value of each index was almost the same between the 2 groups, which indicates that a PD addition in patients who underwent a hepatectomy did not have a significant effect on the value of the vWF level, the ADAMTS13 activity, or the vWF to ADAMTS13 ratio (**Figure 3**A, B, and C).

CASES WITH THROMBOTIC COMPLICATIONS AND THEIR vWF TO ADAMTS13 RATIOS

Neither the patients who underwent a major hepatectomy nor the patients who underwent a PD had hemorrhagic complications within the first 2 weeks following surgery. Although none of the patients who underwent a PD developed thrombotic complications afterward, 3 of the 50 patients who underwent a major hepatectomy (6%) developed clinically significant thrombotic complications within 2 weeks after their respective surgical

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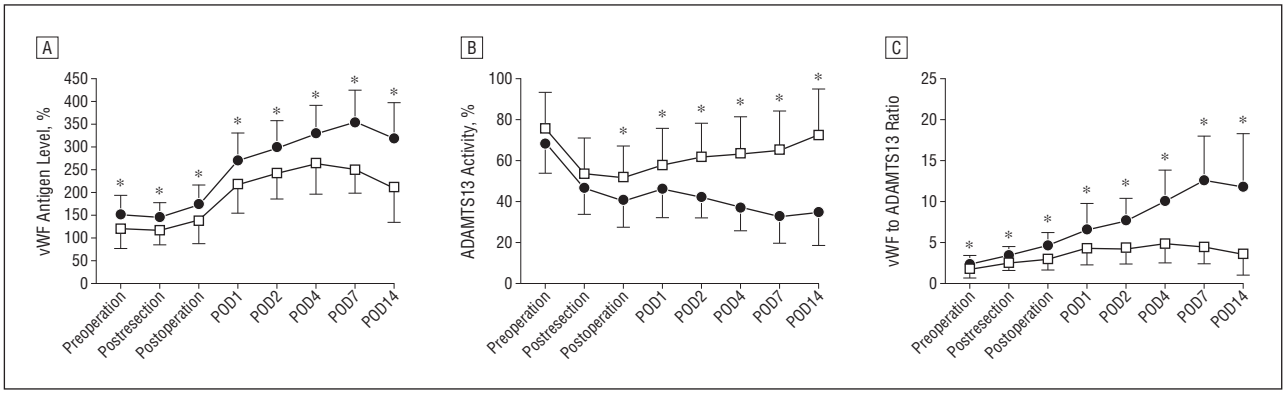

Figure 2. Changes in the plasma von Willebrand factor (vWF) antigen level (A), ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13) activity (B), and the vWF to ADAMTS13 ratio (C) in patients before and after a major hepatectomy (filled circles) or a pancreatoduodenectomy (open squares). Values are expressed as mean values. Error bars indicate SD. $*P<.05$. POD indicates postoperative day.

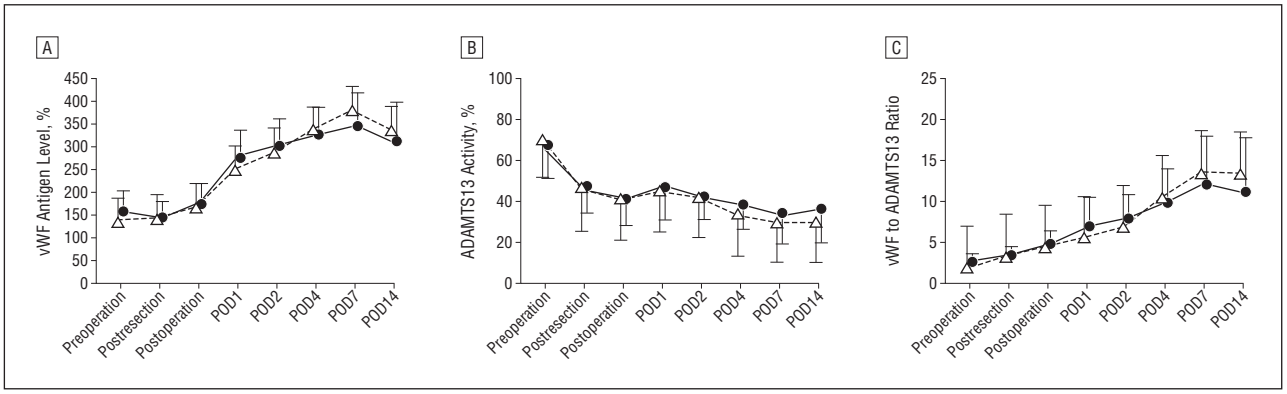

Figure 3. Changes in the plasma von Willebrand factor (vWF) antigen level (A), ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13) activity (B), and the vWF to ADAMTS13 ratio (C) in patients before and after a major hepatectomy without pancreatoduodenectomy (filled circles) or a major hepatectomy with pancreatoduodenectomy (open triangles). Values are expressed as mean values. Error bars indicate SD. $*P<.05$. POD indicates postoperative day.

procedures (**Figure 4**). The vWF to ADAMTS13 ratios in these 3 patients were extremely high before the thrombosis occurred.

Case A was a patient who underwent a right trisectionectomy with resection and reconstruction of the portal vein and the left hepatic artery (Figure 4). This patient was diagnosed as having a portal vein thrombosis during a follow-up computed tomography study on postoperative day 6, and the patient developed liver failure. Two days prior to this diagnosis, this patient's vWF to ADAMTS13 ratio was 14.9.

Case B was a patient who underwent a right trisectionectomy with a segmental resection of the inferior vena cava with reconstruction using an external iliac vein graft. This patient was diagnosed as having an inferior vena cava thrombosis that extended to the renal vein on postoperative day 6. Two days prior to this diagnosis, this patient's vWF to ADAMTS13 ratio was 13.1. Although vascular resection and reconstruction were performed for both cases A and B, there were no technical errors during the 2 surgical procedures. A routine ultrasonography performed immediately after each surgery revealed no thrombotic complications.

Case C was a patient who underwent a right hepatectomy and subsequently developed a cerebral infarction with severe left hemiparesis on postoperative day 3. On the day prior to the diagnosis, this patient's vWF to ADAMTS13 ratio was 13.3.

In all 3 of these patients, the maximum observed vWF to ADAMTS13 ratio exceeded 20 at some point during the first 2 postoperative weeks. Fortunately, all 3 patients recovered and were discharged from the hospital in good condition. There was no incidence of deep venous thrombosis in our study, probably owing to the routine use of compression stockings and to the enforcement of early ambulation for all patients.

THE RELATIONSHIP BETWEEN THE vWF TO ADAMTS13 RATIO AND PREOPERATIVE OR INTRAOPERATIVE VARIABLES

We analyzed the correlations between the vWF to ADAMTS13 ratio on postoperative day 7 and preoperative liver function (ie, the ICG retention rate at 15 minutes), intraoperative factors (operation time and amount of intraoperative blood loss), and remnant liver volume. There were no statistically significant correlations between the vWF to ADAMTS13 ratio and the ICG retention rate at 15 minutes (**Figure 5**A), the operation time (Figure 5B), or the amount of intraoperative blood loss (Figure 5C). However, there was a strong correlation be-

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tween the remnant liver volume and the vWF to ADAMTS13 ratio ($P < .001$) (Figure 5D). The Spearman correlation coefficients between these 2 factors on postoperative day 7 and postoperative day 14 were –0.736 and –0.771, respectively.

COMMENT

The aim of our study was to investigate alterations in the levels of procoagulant/fibrinolytic factors and their relation to the incidence of thrombotic complications during the perioperative period in patients who underwent a major hepatectomy. Our study clearly demonstrated a characteristic profile of vWF level and ADAMTS13 activity after a major hepatectomy. We found that patients who underwent a major hepatectomy exhibit increased plasma vWF antigen levels and reduced plasma ADAMTS13 activity even after postoperative days 7 and 14. The vWF to ADAMTS13 ratio was particularly high in 3 patients who developed clinically significant thrombotic complications that required anticoagulant therapy. Moreover, we also demonstrated that the vWF to ADAMTS13 ratio is strongly correlated with the remnant liver volume.

Endothelial dysfunction is one of the consequences of major surgery, and increased vWF levels are widely accepted as an indicator of endothelial damage and/or dysfunction.[6,7,10] In the present study, the levels of plasma vWF antigen were significantly higher in patients who underwent a major hepatectomy than in patients who underwent a PD. These results suggest that a major hepatectomy may induce more severe endothelial cell damage or dysfunction.

The dynamics of plasma ADAMTS13 activity were strikingly different between patients who underwent a major hepatectomy and patients who underwent a PD. For the patients who underwent a PD, plasma ADAMTS13 activity started quickly on postoperative day 1 and was restored to its preoperative levels by postoperative day 14. In contrast, the level of plasma ADAMTS13 activity in patients who underwent a major hepatectomy continued to decrease throughout the first 2 postoperative weeks. There was an even more distinct difference observed in the vWF to ADAMTS13 ratios between these 2 groups of patients, as shown in Figure 2C. Because previous studies have shown a correlation between high vWF to ADAMTS13 ratios and thrombotic diseases, such as myocardial infarctions,[12] cerebral infarctions,[13] and thrombotic microangiopathies,[14] it is likely that patients who underwent a major hepatectomy have an increased susceptibility for developing thrombosis.

The major organ that produces ADAMTS13 is the liver, and hepatic stellate cells are the primary source of ADAMTS13 production.[25] Figure 5D demonstrates that the sharp increase in the vWF to ADAMTS13 ratio after a major hepatectomy is correlated with the remnant liver volume. Thus, it is possible that the levels of circulating ADAMTS13 are significantly reduced because of a substantial reduction in liver volume. Other factors, such as the ICG retention rate at 15 minutes, the operation time, and the amount of intraoperative blood loss, did not correlate with the vWF to ADAMTS13 ratio. To our knowledge, this is the first report that showed a clear correlation between the vWF to ADAMTS13 ratio and the remnant liver volume.

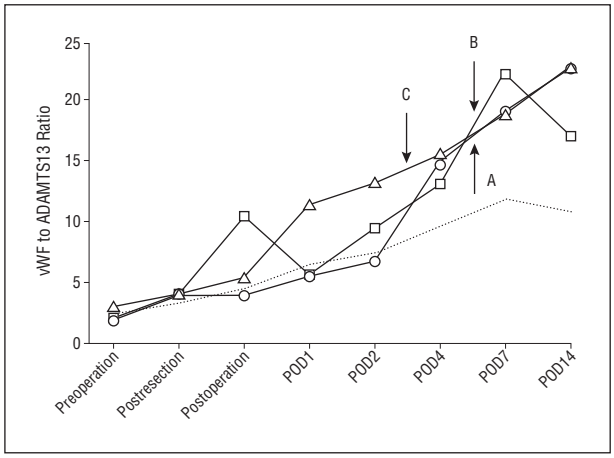

Figure 4. Changes in the von Willebrand factor (vWF) to ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13) ratio in 3 cases with clinically significant thrombotic complications (cases A [open circles], B [open squares], and C [open triangles]). The arrows indicate the postoperative day (POD) that thrombotic complications occurred. The dotted line indicates the mean value for cases without thrombotic complications.

In our series of hepato-pancreato-biliary surgical procedures, only 3 patients developed clinically significant thrombotic complications that required anticoagulant therapy. These complications all occurred after a major hepatectomy, and no thromboses were observed after a PD. In the patients who experienced complications, the levels of conventionally measured procoagulant/fibrinolytic factors, such as prothrombin time, coagulation factor VII, fibrinogen, activated partial thromboplastin time, platelet count, thrombin-antithrombin III complex, and plasmin-α2 plasmin inhibitor complex, were comparable to those observed in patients without thrombotic complications (data not shown). The mean vWF to ADAMTS13 ratio in healthy volunteers has been reported to be 0.51 to 2.43.[26] The preoperative vWF to ADAMTS13 ratios in this cohort were close to this value in both groups of patients. However, the vWF to ADAMTS13 ratio was extraordinary high in the 3 patients who developed postoperative thrombotic complications (Figure 4). The maximum vWF to ADAMTS13 ratio observed for these patients exceeded 20, which was not observed in patients who did not develop thrombosis (Figure 4). Despite the small sample size, our data imply a potential association between the incidence of thrombotic complications and elevated vWF to ADAMTS13 ratios following a major hepatectomy. It should be noted, however, that thrombosis formation may lead to endothelial damage and may increase the level of the vWF to ADAMTS13 ratio. Further large-scale data collection will be required to elucidate the correlation between the vWF to ADAMTS13 ratio and thrombotic complications and to determine the optimal ratio at which prophylactic anticoagulation therapy should be initiated.

Based on our current observations, anticoagulation therapy should be used for patients with elevated vWF

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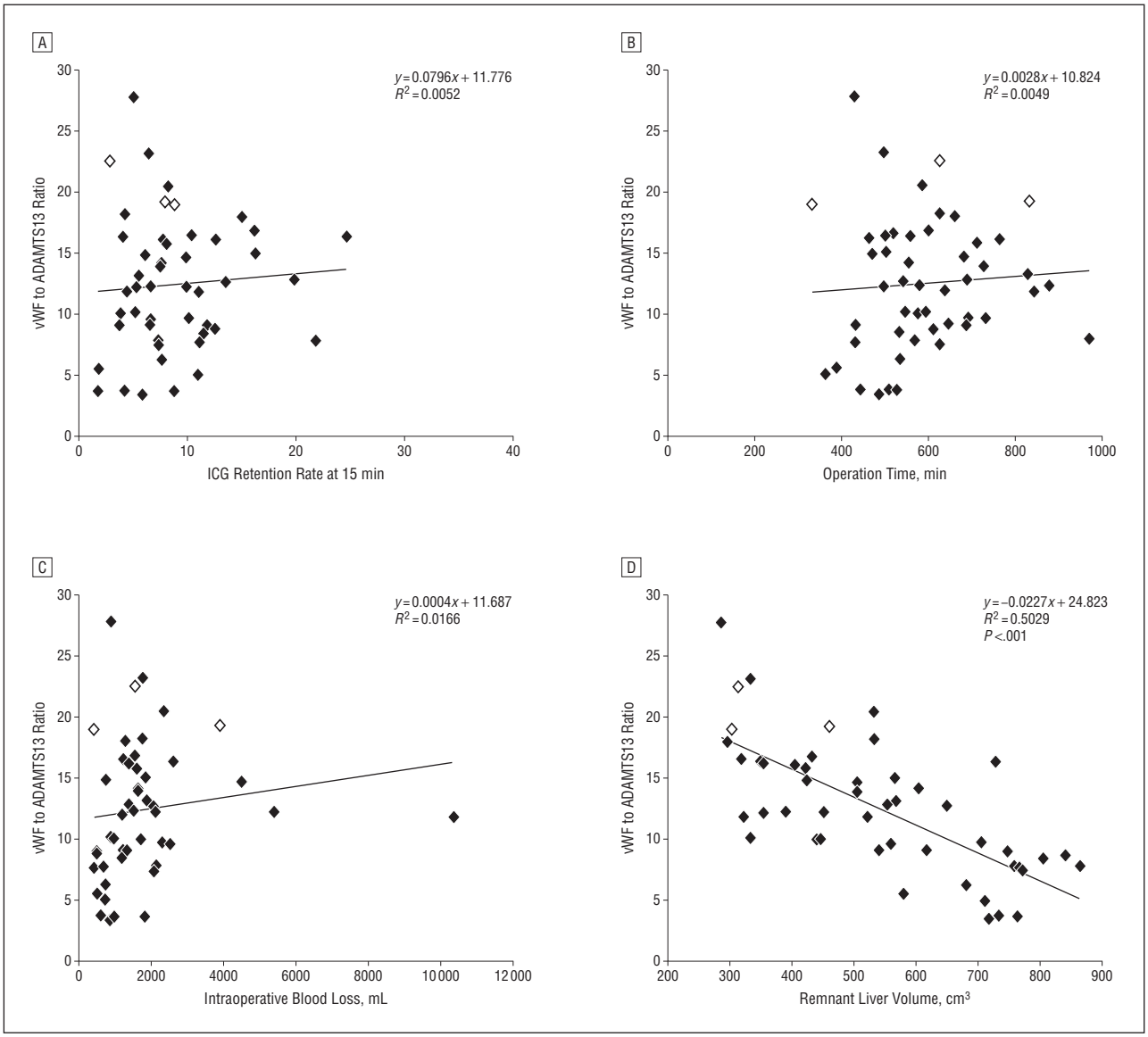

Figure 5. Correlations between the von Willebrand factor (vWF) to ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13) ratio and indocyanine green (ICG) retention rate at 15 minutes (A), the vWF to ADAMTS13 ratio and operation time (B), the vWF to ADAMTS13 ratio and intraoperative blood loss (C), and the vWF to ADAMTS13 ratio and remnant liver volume (D), on postoperative day 7 in 50 patients who underwent a major hepatectomy (filled diamonds). The open diamonds indicate patients with thrombotic complications.

to ADAMTS13 ratios during the course of postoperative treatment. The standard prophylactic treatment of choice for thrombotic events might include the systemic administration of warfarin potassium or heparin sodium.[27] However, because of the risk of gross hemorrhage with these treatments, it is possible that prophylactic supplementation of ADAMTS13 to normalize the vWF to ADAMTS13 ratio may also decrease the incidence of thrombotic complications following a major hepatectomy without increasing the incidence of hemorrhagic events.

In summary, our study demonstrated distinct profiles of procoagulant/fibrinolytic factors in patients who underwent a major hepatectomy and patients who underwent a PD. In addition, we provide evidence that abnormally high vWF to ADAMTS13 ratios in patients who underwent a major hepatectomy may indicate a potential increased risk of thrombotic complications. Further prospective studies are necessary to examine the importance of vWF to ADAMTS13 ratios and to establish the appropriate therapeutic protocols to normalize vWF to ADAMTS13 ratios and prevent severe thrombotic complications.

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Correspondence: Masato Nagino, MD, Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan (nagino@med.nagoya-u.ac.jp).
Author Contributions: *Study concept and design:* Kobayashi, Yokoyama, Matsushita, Kainuma, Ebata, Igami,

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ADAMTS13

The Surgeon's Friend or Foe

Control of bleeding is an essential requirement of surgery, and the risks of excessive bleeding are of major concern to surgeons. This is especially true for liver surgeons in view of the coagulopathy associated with the lack of essential clotting factors in patients with decompensated liver disease. However, it would now appear that the lack of certain factors produced by the liver may, in fact, also render the patient hypercoagulable.

The role of ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13) in hemostasis has been extensively documented in the hematology literature. In contrast, ADAMTS13 has hardly been noticed on the surgical radar. ADAMTS13 is a specific metalloproteinase that is responsible for cleaving the multimeric form of von Willebrand factor, thus preventing platelet aggregation and thrombus formation.[1] Conversely, in the absence of ADAMTS13 activity, or with a profound deficiency of ADAMTS13, due to either genetic mutations or autoimmune inhibitors, ultralarge von Willebrand factor produced by vascular endothelial cells accumulate and induce widespread microvascular thrombosis characteristic of thrombotic thrombocytopenic purpura.

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