

# World Journal of *Gastroenterology*

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## Observational Study

**Association between ADAMTS13 activity–VWF antigen imbalance and the therapeutic effect of HAIC in patients with hepatocellular carcinoma**

Hiroaki Takaya, Tadashi Namisaki, Kei Moriya, Naotaka Shimozato, Kosuke Kaji, Hiroyuki Ogawa, Koji Ishida, Yuki Tsuji, Daisuke Kaya, Hirotestu Takagi, Yukihisa Fujinaga, Norihisa Nishimura, Yasuhiko Sawada, Hideto Kawaratani, Takemi Akahane, Masanori Matsumoto, Hitoshi Yoshiji

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**Abstract****BACKGROUND**

Prediction of HAIC treatment response is important for improving the prognosis in patients with hepatocellular carcinoma (HCC). The progression of HCC is related to hypercoagulability and angiogenesis. It is known that ADAMTS13 and von Willebrand factor (VWF) are related to hypercoagulability. In addition, previous study reported that the association between ADAMTS13 and VWF, and angiogenesis *via* vascular endothelial growth factor (VEGF). Recently, ADAMTS13 and VWF have been associated with the prognosis in patients with various kinds of cancer undergoing chemotherapy.

**AIM**

To investigate whether ADAMTS13 and VWF become useful biomarkers of treatment response in HCC patients before the initiation of HAIC treatment.

**METHODS**

Seventy-two patients were enrolled in this study. ADAMTS13 activity (ADAMTS13:AC), VWF antigen (VWF:Ag) and VEGF levels were determined *via* enzyme-linked immunosorbent assay. Univariable and multivariable analyses were performed to determine the predictive factors of treatment response in patients with HCC undergoing HAIC treatment.

study protocol was approved by the Ethics Committee of Nara Medical University.

**Informed consent statement:** All study participants or their legal guardians provided informed written consent prior to study enrollment.

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## RESULTS

ADAMTS13:AC levels in HCC patients with stable disease (SD) + partial response (PR) of HAIC treatment were significantly higher than those with progressive disease (PD) ( $P < 0.05$ ). In contrast, VWF:Ag/ADAMTS13:AC ratio and VEGF levels in HCC patients with SD + PR were significantly lower than those with PD (both  $P < 0.05$ ). Patients with high VWF:Ag/ADAMTS13:AC ratio ( $> 2.7$ ) had higher VEGF levels than those with low ratio ( $\leq 2.7$ ). Multivariable analysis revealed that VWF:Ag/ADAMTS13:AC ratio was a predictive factor of HAIC treatment response.

## CONCLUSION

VWF:Ag/ADAMTS13:AC ratio may become a useful biomarker of treatment response in HCC patients before the initiation of HAIC treatment.

**Key Words:** ADAMTS13; Von Willebrand factor; Vascular endothelial growth factor; Biomarkers; Hepatocellular carcinoma; HAIC

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**Core Tip:** The prediction of HAIC treatment response is needed to improve the prognosis in patients with hepatocellular carcinoma (HCC). Von Willebrand factor antigen (VWF:Ag)/ADAMTS13 activity (ADAMTS13:AC) ratio was significantly lower in HCC patients with stable disease + partial response than those with progressive disease. VWF:Ag/ADAMTS13:AC ratio become a useful biomarker to predict HAIC treatment response.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) has one of the highest mortality rates of any cancer<sup>[1,2]</sup>. In Japan, HCC management follows the consensus-based clinical practice guidelines of the Japan Society of Hepatology (JSH)<sup>[3]</sup>. JSH recommends that advanced HCC patients with vascular invasion or more than four tumors should undergo chemotherapy such as HAIC or molecular-targeted drugs<sup>[3]</sup>. However, it is important to predict HAIC response before deciding on the appropriate chemotherapy protocol for improving the prognosis in patients with HCC.

ADAMTS13 is a metalloproteinase that is exclusively produced from hepatic stellate cells adjacent to endothelial cells (ECs)<sup>[4-8]</sup>. It specifically cleaves multimeric von Willebrand factor (VWF) between the Tyr1605 and Met1606 residues in the A2 domain<sup>[4-7]</sup>. VWF is synthesized in vascular ECs and released into the plasma as unusually large multimers<sup>[9]</sup>. During ADAMTS13 enzyme–VWF substrate imbalance, VWF is improperly cleaved, resulting in the accumulation of multimers and the induction of platelet thrombi formation in the microvasculature under high shear-stress conditions<sup>[10]</sup>. In other words, ADAMTS13 enzyme–VWF substrate balance is related to hypercoagulability. Furthermore, the blood coagulation cascade is related to cancer progression<sup>[11,12]</sup>, and our previous study has reported that ADAMTS13 enzyme–VWF substrate imbalance becomes worse based on HCC progression<sup>[13,14]</sup>.

Angiogenesis plays an important role in HCC progression<sup>[15]</sup>. A recent study has reported that ADAMTS13 enzyme–VWF substrate imbalance is related to angiogenesis<sup>[16]</sup> as well as hypercoagulability and is associated with the prognosis in patients with various kinds of cancer undergoing chemotherapy<sup>[14,17]</sup>.

In the present study, we investigated the relationship between ADAMTS13

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enzyme–VWF substrate balance and HCC in patients undergoing HAIC treatment. In addition, we sought to determine whether ADAMTS13 and VWF may become predictive biomarkers of treatment response in HCC patients before starting HAIC treatment.

## MATERIALS AND METHODS

### Patients

This retrospective observational study included patients with HCC who underwent HAIC treatment from December 2009 to March 2019. Patients with HCC had no vascular invasion or less than four tumors were excluded. A total of 72 patients with HCC were included in this study. HAIC treatment was performed according to the Moriya method<sup>[18,19]</sup>, which features a bi-monthly protocol that is simple and easy to manage. The patients underwent dynamic computed tomographic scanning or dynamic magnetic resonance imaging at various points, namely before starting HAIC treatment, 1 mo after commencement of the treatment, and every 2 mo thereafter. HAIC treatment responses were evaluated according to modified response evaluation criteria in solid tumors. This study had no patient with infection, uncontrolled hepatic encephalopathy, ascites, or gastroesophageal varices. This study was approved by the local ethics committee in Nara Medical University and was performed according to the ethical standards laid down in the Declaration of Helsinki. Informed consent was obtained from all patients included in the study.

### Determination of ADAMTS13 activity and VWF antigen levels

We collected blood samples from each patient at the time of admission, during their hospital stay, or during regular outpatient treatment before starting HAIC treatment. The plastic tubes with 0.38% sodium citrate was used to store these samples. We centrifuged these samples at  $3000 \times g$  at 4 °C for 15 min to prepare the plasma and stored the plasma at -80 °C until analysis. Plasma ADAMTS13 activity (ADAMTS13:AC) was determined using a sensitive chromogenic enzyme-linked immunosorbent assay (ELISA) (Kainos Laboratories Inc., Tokyo, Japan)<sup>[20]</sup> to show a normal value of  $99\% \pm 22\%$ . Plasma VWF antigen (VWF:Ag) levels were measured *via* sandwich ELISA using a rabbit anti-human VWF polyclonal antiserum (Dako, Glostrup, Denmark). The normal VWF:Ag value is  $102\% \pm 33\%$ <sup>[21]</sup>.

### VEGF measurements

VEGF levels were determined using a commercially available kit (Immunoassay Kits, RayBiotech Inc., United States). The detection limit of VEGF was < 10 pg/mL.

### Statistical analysis

The Mann–Whitney *U*-test and the Fisher's exact test were performed to analyze differences between study groups and categorical data, respectively. Univariable and multivariable analysis were performed to evaluate HAIC response for HCC. Logistic regression analysis was performed to determine independent response factors, and data were expressed as median (interquartile range). A two-tailed *P* value of < 0.05 was considered significant. Analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Japan), a graphical user interface of R version 2.13.0 (The R Foundation for Statistical Computing, Vienna, Austria), and a modified version of R commander (version 1.6-3) that includes statistical functions that are frequently used in biostatistics<sup>[22]</sup>.

## RESULTS

### Clinical characteristics of the HCC patients

**Table 1** showed the clinical characteristics of HCC patients. The median period of HAIC treatment was 121 (range 41–218) d and the median age of HCC patients was 70.5 (range 64.2–76.1) years. Of the study population (57 males, 15 females), 17 patients had hepatitis B virus infection, 36 had hepatitis C virus infection, 10 had alcohol abuse, 4 had non-alcoholic steatohepatitis, and 5 had others. The median maximum tumor size was 3.3 (range 2.2–5.0) cm. Tumors numbering 1, 2, 3, 4, or > 4 were 9, 5, 6, 2, and 50, respectively. Thirty-one patients had vascular invasion and no patient had distant metastasis. Serum alpha-fetoprotein (AFP), des-γ-carboxy prothrombin, and lens

**Table 1 Hepatocellular carcinoma patients' characteristics between stable disease + partial response and progressive disease with hepatic arterial infusion chemotherapy**

Variable	Total (n = 72)	SD + PR (n = 41)	PD (n = 31)	P value
Age (yr)	70.5 (64.2–76.1)	72.0 (66.4–76.4)	67.8 (58.9–75.1)	NS
Sex (male/female)	57/15	32/9	25/6	NS
Etiology (HBV/HCV/alcohol/NASH/others)	17/36/10/4/5	6/23/5/4/3	11/13/5/0/2	NS
Albumin (g/dL)	3.2 (3.0–3.6)	3.3 (3.0–3.6)	3.2 (3.0–3.7)	NS
Prothrombin time (%)	76.0 (60.5–85.3)	78.0 (57.0–86.0)	73.0 (63.5–83.0)	NS
Total bilirubin (mg/dL)	1.2 (0.8–2.1)	1.2 (0.7–2.1)	1.2 (0.8–2.2)	NS
Platelet count ( $\times 10^4/\text{mm}^3$ )	10.4 (7.1–14.9)	10.8 (7.0–13.2)	10.1 (7.6–17.1)	NS
AFP (ng/mL)	95.3 (17.9–1162.5)	101.0 (21.2–931.5)	87.1 (13.2–1349.2)	NS
DCP (mAU/mL)	359.5 (58.0–5277.5)	348 (42.3–1542.8)	609.0 (88.2–279.4)	NS
AFP-L3% (%)	33.7 (7.7–73.4)	34.3 (6.9–73.4)	22.2 (8.1–68.8)	NS
Maximum tumor size (cm)	3.3 (2.2–5.0)	3.0 (2.0–5.0)	3.5 (2.9–3.5)	NS
Tumor number (1/2/3/4/> 4)	9/5/6/2/50	5/4/3/2/27	4/1/3/0/23	NS
Vascular invasion (present/absent)	31/41	20/21	11/20	NS
Treatment period (days)	121 (41–218)	191 (120–311)	40.0 (26–61)	< 0.05

Data are expressed as median (interquartile range). *P* values represent comparisons between SD + PR and PD with hepatic arterial infusion chemotherapy. SD: Stable disease; PR: Partial response; PD: Progressive disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NASH: Non-alcoholic steatohepatitis; AFP: Alpha-fetoprotein; DCP: Des- $\gamma$ -carboxy prothrombin; AFP-L3%: Lens culinaris agglutinin-reactive alpha-fetoprotein.

culinaris agglutinin-reactive fraction of AFP levels were 95.3 (17.9–1162.5) ng/mL, 359.5 (58.0–5277.5) mAU/mL, and 33.7% (7.7%–73.4%), respectively. We investigated the HAIC treatment response between stable disease (SD) + partial response (PR) and progressive disease (PD). No significant differences were observed in HCC patients' characteristics between SD + PR and PD, except for treatment periods.

### Plasma ADAMTS13:AC and VWF:Ag levels

ADAMTS13:AC levels in HCC patients with SD + PR were significantly higher than those with PD ( $P < 0.05$ ) (Figure 1A). VWF:Ag levels were no different between patients with SD + PR and PD (Figure 1B). The ratio of VWF:Ag to ADAMTS13:AC (VWF:Ag/ADAMTS13:AC ratio) in patients with SD + PR was significantly lower than those with PD ( $P < 0.05$ ) (Figure 1C).

### Plasma VEGF levels

VEGF levels in HCC patients with SD + PR were significantly lower than those with PD ( $P < 0.05$ ) (Figure 2A). Patients were categorized into two groups according to receiver operating characteristic (ROC) cut-off VEGF: Low,  $\leq 100$  and high,  $> 100$ . Patients with high VEGF levels also had higher platelet levels than those with low VEGF (Figure 2B). Patients were categorized into two groups according to ROC cut-off VWF:Ag/ADAMTS13:AC ratio: Low,  $\leq 2.7$  and high,  $> 2.7$ . Patients with high VWF:Ag/ADAMTS13:AC ratio had higher VEGF levels than those with low ratio (Figure 2C).

### Predictive factors for HAIC response

Patients were categorized into two groups according to ROC cut-off. Univariable analysis showed that HAIC treatment response is associated with prothrombin time (PT), VEGF, and VWF:Ag/ADAMTS13:AC ratio (Table 2). To determine the predictive factors of HAIC response, multivariable analysis was performed using PT, VEGF, and VWF:Ag/ADAMTS13:AC ratio, with these factors showing  $P < 0.05$  in univariable analysis. VWF:Ag/ADAMTS13:AC ratio was significantly associated with HAIC treatment response *via* multivariable analysis (Table 2). ROC analysis showed that VWF:Ag/ADAMTS13:AC ratio is sensitivity of 53.7%, specificity of 87.1%, and area under the curve of 0.715.

**Table 2 Predictive factors for response of hepatic arterial infusion chemotherapy in patients with hepatocellular carcinoma**

Variable	Univariable analysis		Multivariable analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Age > 65 yr	2.61 (0.905–7.5)	0.076		
Sex (male vs female)	0.853 (0.268–2.72)	0.788		
Albumin > 2.8 g/dL	1.40 (0.404–4.85)	0.596		
Prothrombin time > 80%	2.68 (1.010–7.10)	0.0469	1.98 (0.654–5.96)	0.227
Total bilirubin > 2 mg/dL	0.896 (0.317–2.53)	0.836		
Platelet count > 20 × 10 <sup>4</sup> /μL	1.57 (0.268–9.16)	0.618		
AFP > 50 ng/mL	0.523 (0.194–1.41)	0.199		
DCP > 20 mAU/mL	0.381 (0.0938–1.55)	0.177		
AFP-L3% > 20%	1.33 (0.491–3.62)	0.572		
VEGF > 100 pg/mL	0.223 (0.0802–0.618)	0.0039	0.370 (0.127–1.07)	0.0677
Maximum tumor size > 2.3 cm	0.414 (0.130–1.32)	0.137		
Tumor number > 2	1.07 (0.261–4.35)	0.928		
Vascular invasion (present/absent)	1.73 (0.665–4.51)	0.261		
ADAMTS13:AC > 75%	1.25 (0.355–4.41)	0.727		
VWF:Ag > 260%	0.711 (0.279–1.81)	0.476		
VWF:Ag/ADAMTS13:AC > 2.7	0.141 (0.0418–0.476)	0.0016	0.176 (0.0493–0.631)	0.00766

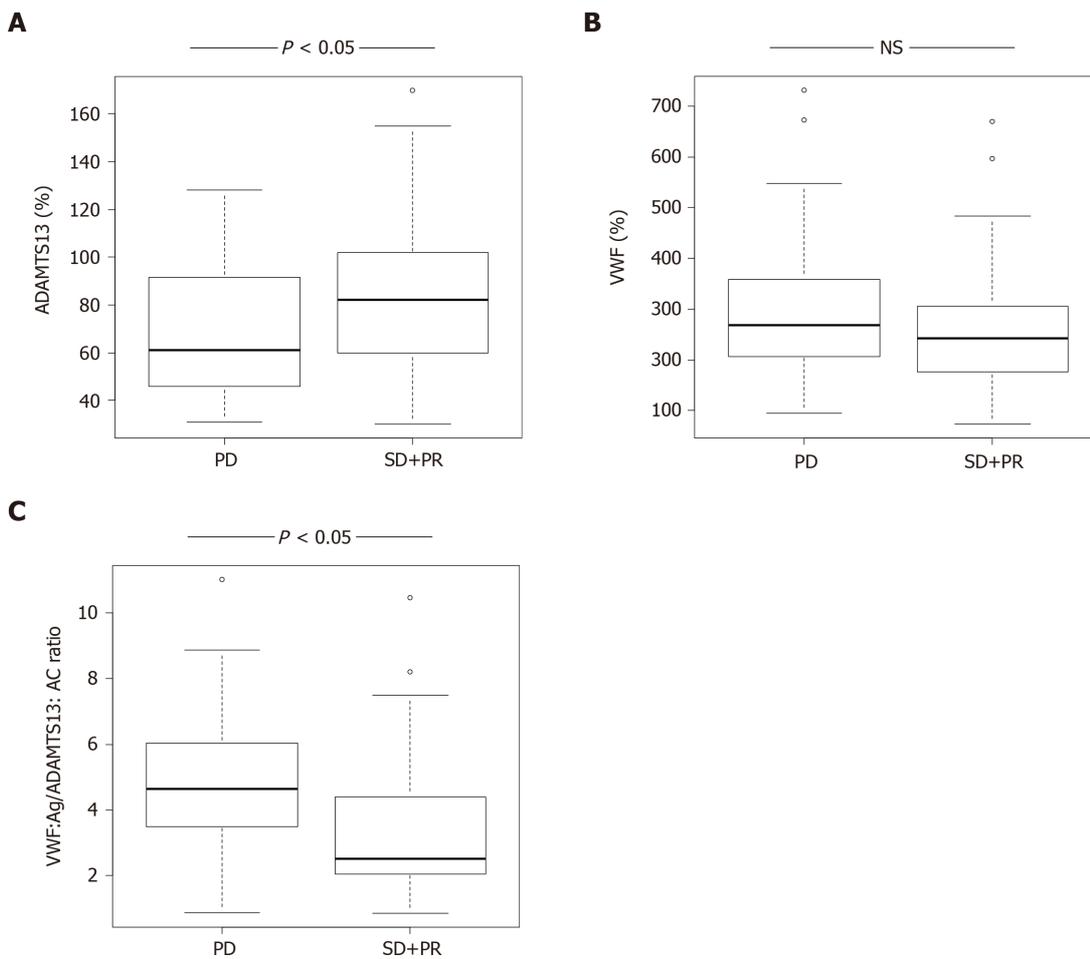
OR: Odds ratio; CI: Confidence interval; AFP: Alpha-fetoprotein; DCP: Des-γ-carboxy prothrombin; AFP-L3%: Lens culinaris agglutinin-reactive alpha-fetoprotein; VEGF: Vascular endothelial growth factor; ADAMTS13: A disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13; ADAMTS13:AC: ADAMTS13 activity; VWF: Von Willebrand factor; VWF:Ag: VWF antigen; VWF:Ag/ADAMTS13:AC ratio: Ratio of VWF:Ag to ADAMTS13:AC.

## DISCUSSION

We suggest that VWF:Ag/ADAMTS13:AC ratio is a potential biomarker for HAIC treatment response in the present study. It is well-known that this ratio is related to the coagulation cascade<sup>[10]</sup>, which in turn plays an important role in the cancer development, including HCC<sup>[11,12]</sup>. Previous studies have reported that ADAMTS13 enzyme–VWF substrate imbalance is associated with cancer progression, prognosis of patients with various kinds of cancer, and response to chemotherapy<sup>[17,23]</sup>. Our previous study reported that VWF:Ag<sup>[7]</sup> and VWF:Ag/ADAMTS13:AC ratio<sup>[13]</sup> are predictive and detective factors of HCC in patients with cirrhosis, respectively. Moreover, a study has reported that the association between ADAMTS13:AC and VWF:Ag, and the treatment efficiency of molecular-targeted drugs<sup>[14]</sup>.

It is well-known that angiogenesis is related to the pathophysiology of HCC development<sup>[15]</sup> and that VEGF plays an important role in angiogenesis<sup>[15]</sup>. Recently, studies have reported that VWF reduces VEGF-dependent angiogenesis *via* multiple intracellular and extracellular pathways involving integrin αvβ3 and angiopoietin-2<sup>[16,24,25]</sup> and that ADAMTS13 cleaves VWF and promotes VEGFR-2 phosphorylation, as the result, induces angiogenesis. This in turn results in enhancement of VEGF expression<sup>[26]</sup>. Xu have reported that the important role of ADAMTS13 enzyme–VWF substrate balance in the regulation of blood vessel formation<sup>[16]</sup>. A previous study has reported that HAIC treatment decreases VEGF levels in patients with advanced HCC<sup>[27]</sup>. Therefore, VWF:Ag/ADAMTS13:AC ratio may be associated with HAIC treatment response *via* VEGF and angiogenesis.

Furthermore, anti-platelet therapy inhibits VEGF that induces HCC development<sup>[28]</sup>. A recent study has reported that anti-platelet therapy for cirrhotic patients prevents HCC development<sup>[29]</sup> and prolongs survival time in hepatitis B virus mouse model of chronic liver disease<sup>[28]</sup>. ADAMTS13 enzyme–VWF substrate imbalance induces platelet thrombi formation<sup>[10]</sup>. In other words, ADAMTS13 enzyme–VWF substrate imbalance, VEGF, angiogenesis, and hypercoagulability are closely related to the cancer progression, including HCC. A previous study has found that VEGF is



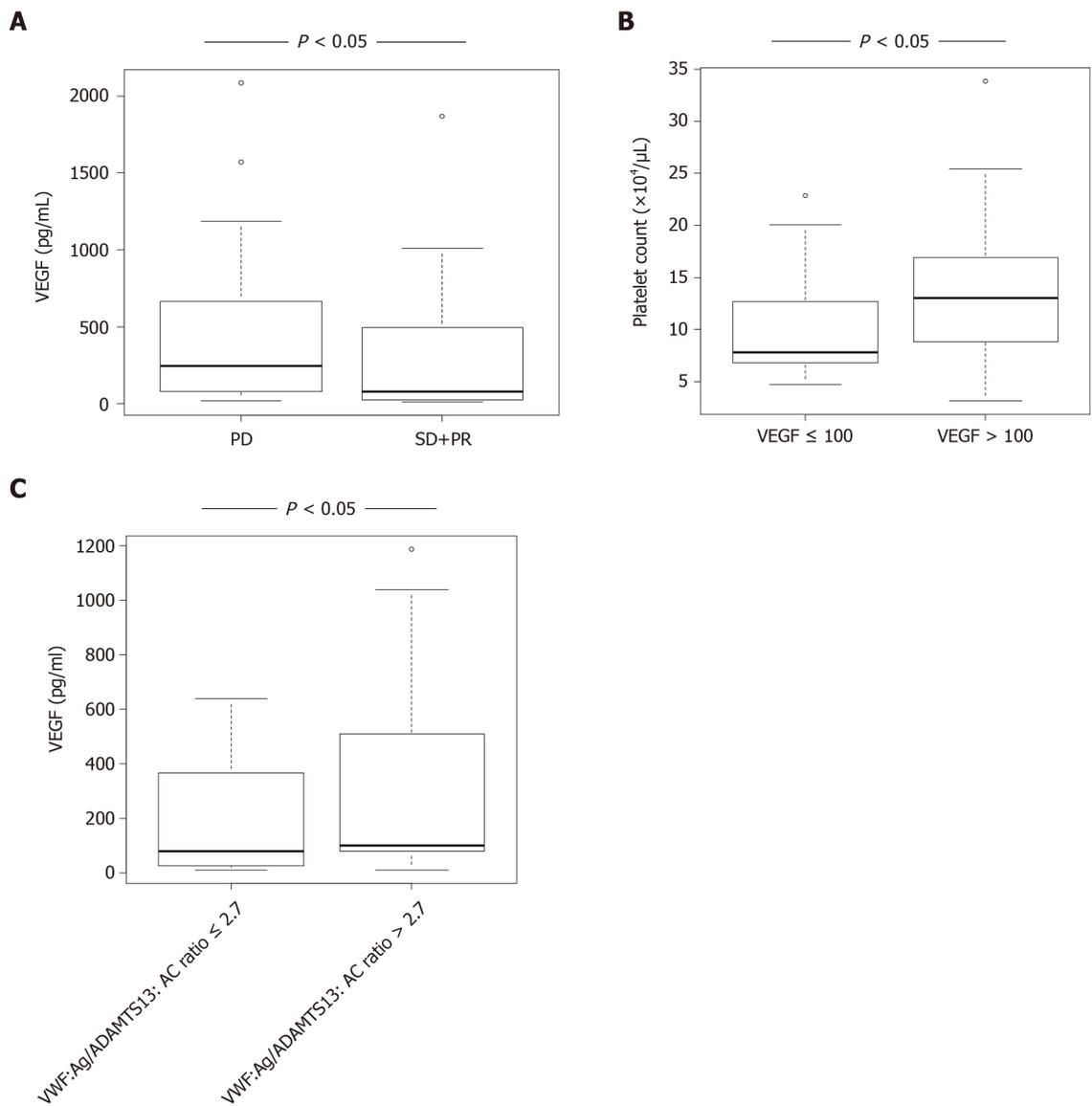
**Figure 1 Plasma ADAMTS13:AC and VWF:Ag levels in patients with hepatocellular carcinoma receiving hepatic arterial infusion chemotherapy treatment.** A: ADAMTS13 activity (ADAMTS13:AC) levels were significantly higher in hepatocellular carcinoma patients receiving hepatic arterial infusion chemotherapy treatment with stable disease (SD) + partial response (PR) than in those with progressive disease (PD) ( $P < 0.05$ ); B: VWF antigen (VWF:Ag) levels were not different between patients with SD + PR and PD; C: VWF:Ag/ADAMTS13:AC ratio was significantly lower in patients with SD + PR than in those with PD ( $P < 0.05$ ). SD: Stable disease; PR: Partial response; PD: Progressive disease; ADAMTS13: A disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13; ADAMTS13:AC: ADAMTS13 activity; VWF: Von Willebrand factor; VWF:Ag: VWF antigen; VWF:Ag/ADAMTS13:AC ratio: Ratio of VWF:Ag to ADAMTS13:AC.

associated with HAIC treatment response and prognosis<sup>[30]</sup>. Our study reported the association between VWF:Ag/ADAMTS13:AC ratio and HAIC treatment response; however, our analysis indicated that VEGF is not a predictive factor of HAIC treatment response. VWF:Ag/ADAMTS13:AC ratio may become a more useful to predict HAIC treatment response than VEGF.

Our study has some limitations that include a small sample size and short observation. Cirrhotic patients with advanced HCC occasionally develop thrombosis or inflammation (*e.g.*, portal thrombosis, and bacterial overgrowth and translocation). When VWF:Ag/ADAMTS13:AC ratio is used as a biomarker of HAIC treatment response, thrombosis and inflammation may affect the values<sup>[4,23,31]</sup>. In addition, VWF:Ag/ADAMTS13:AC ratio has high specificity but moderate sensitivity to predict HAIC treatment response. Therefore, we should continue to investigate high-sensitivity biomarkers.

## CONCLUSION

In summary, VWF:Ag/ADAMTS13:AC ratio is an independent predictive factor for response in patients with HCC undergoing HAIC treatment.



**Figure 2 Plasma vascular endothelial growth factor levels in patients with hepatocellular carcinoma receiving hepatic arterial infusion chemotherapy treatment.** A: Vascular endothelial growth factor (VEGF) levels were significantly lower in hepatocellular carcinoma patients with stable disease + partial response than in those with progressive disease ( $P < 0.05$ ); B: Patients with high VEGF levels ( $> 100$ ) had higher platelet levels than those with low VEGF levels ( $\leq 100$ ) ( $P < 0.05$ ); C: Patients with high Von Willebrand factor antigen (VWF:Ag)/ADAMTS13 activity (ADAMTS13:AC) ratio ( $> 2.7$ ) had higher VEGF levels than those with low VWF:Ag/ADAMTS13:AC ratio ( $\leq 2.7$ ). VEGF: Vascular endothelial growth factor; SD: Stable disease; PR: Partial response; PD: Progressive disease; ADAMTS13: A disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13; ADAMTS13:AC: ADAMTS13 activity; VWF: Von Willebrand factor; VWF:Ag: VWF antigen; VWF:Ag/ADAMTS13:AC ratio: Ratio of VWF:Ag to ADAMTS13:AC.

## ARTICLE HIGHLIGHTS

### Research background

Predicting HAIC treatment response is important for improving the prognosis of hepatocellular carcinoma (HCC) patients.

### Research motivation

ADAMTS13 and von Willebrand factor (VWF) have been associated with the prognosis in patients with various kinds of cancer receiving chemotherapy.

### Research objectives

The present study was investigated whether ADAMTS13 and VWF become useful biomarkers of treatment response in HCC patients before the initiation of HAIC treatment.

**Research methods**

Multivariable analysis was performed to determine the predictive factors of HAIC treatment response in patients with HCC.

**Research results**

VWF antigen (VWF:Ag)/ADAMTS13 activity (ADAMTS13:AC) ratio predicted HAIC treatment response in multivariable analysis.

**Research conclusions**

VWF:Ag/ADAMTS13:AC ratio may be a useful biomarker of treatment response in patients with HCC before HAIC treatment.

**Research perspectives**

VWF:Ag/ADAMTS13:AC ratio has high specificity to predict HAIC treatment response. On the other hand, this biomarker has moderate sensitivity. Therefore, we should continue to investigate high-sensitivity biomarkers.

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