

von Willebrand Factor Antigen Predicts Outcomes in Patients after Liver Resection of Hepatocellular Carcinoma

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Background/Aims: von Willebrand factor antigen (vWF-Ag) is a noninvasive predictor of portal hypertension that serves as a negative prognostic marker in various malignancies. Increased portal hypertension is associated with higher postoperative morbidity and decreased survival after hepatectomy. The purpose of this study was to determine the correlation between vWF-Ag, postoperative morbidity and oncological outcome. **Methods:** This analysis includes 55 patients who underwent liver resection for hepatocellular carcinoma (HCC) between 2008 and 2015 with available preoperative vWF-Ag levels. The primary endpoints were postoperative complications and long-term outcome, including overall and disease-free survival. **Results:** The median plasma level of vWF-Ag was 191% (range, 162.5% to 277%). There was a significant correlation between vWF-Ag levels and tumor size in the resected specimens ($p=0.010$, $r=0.350$). Patients who developed any grade of postoperative complication had significantly higher preoperative vWF-Ag levels (216% [range, 178% to 283.25%] vs 176% [range, 148% to 246%], $p=0.041$). Median overall survival was 39.8 months in patients with high vWF-Ag levels ($\geq 191\%$) compared with 73.4 months in patients with low levels ($<191\%$, $p=0.007$). Of note, there was a remarkable disparity in the number of patients who died of HCC with low versus high vWF-Ag levels (14.8% vs 28.6%, $p=0.011$). **Conclusions:** vWF-Ag may serve as a prognostic marker for the outcome of patients undergoing liver resection for HCC that is closely connected to tumor size, postoperative complication rate and long-term outcome. (**Gut Liver 2020;14:218-224**)

Key Words: von Willebrand factor; Outcome; Hepatectomy;

Carcinoma, hepatocellular

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most cause of cancer-related death and its incidence and mortality is increasing.¹⁻⁴ Liver resection is the first-line treatment for patients with solitary HCC, however as in most cases HCC develops in an established liver disease,² resection is only recommended in patients with well-preserved liver function, defined as normal bilirubin with either hepatic venous pressure gradient (HVPG) ≤ 10 mm Hg or platelet count $\geq 100,000/\text{mL}$.⁵ Even though outcome of liver resection has improved significantly over the last decades,⁶ patients still face a considerable morbidity and mortality,⁷ thus prognostic parameters to determine outcome are urgently warranted.

It has been shown that von Willebrand factor antigen (vWF-Ag) is a simple and noninvasive predictor of clinically significant portal hypertension (CSPH; HVPG ≥ 10 mm Hg), that predicts survival and decompensation in patients with liver cirrhosis, independently of Child-Pugh and Model for End-Stage Liver Disease (MELD) score.⁸ Additionally vWF plays a role in platelet-tumor cells interactions, angiogenesis and apoptosis.⁹ Several studies have shown elevated plasma vWF-Ag levels in both hematologic and non-hematologic malignancies.¹⁰⁻¹² Thus vWF-Ag may also serve as a negative prognostic marker for neoplastic disorders.

The aim of the study was to investigate the association between preoperatively measured vWF-Ag levels with postoperative morbidity and oncological outcome defined as disease-free survival (DFS) and overall survival (OS) in patients undergoing

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hepatectomy for HCC.

MATERIALS AND METHODS

1. Patients

This is a retrospective study including all patients undergoing primary liver resection for HCC with curative intent between 2008 and 2015, who were classified Child-Pugh A and had preoperative vWF-Ag, indocyanine green (ICG)-clearance and HVPG measurements as part of their routine work-up. All patients underwent staging computer tomography of the liver, abdomen and thorax before surgery. Additional magnetic resonance imaging of the liver was performed in most patients. Patients were followed routinely at least every 6 months at the outpatient clinic of the Department of General Surgery, Medical University of Vienna. The study was approved by the Ethics Committee of the Medical University of Vienna and was in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonized Tripartite guideline for good clinical practice (IRB number: 1603/2013). Written informed consent was waived.

2. Serological tests

For all patients routine serological tests were performed before surgery: hematology, biochemistry (bilirubin, albumin, creatinine, aminotransferases, albumin, alkaline phosphatase, γ glutamyl-transpeptidase), coagulation parameters (prothrombin time, INR), α -fetoprotein (AFP) and C-reactive protein (CRP).

Plasma levels of vWF-Ag and factor VIII were measured as described previously¹³ using a fully automated STA analyzer and vWF-Liatest (Diagnostica Stago, Paris, France). According to their vWF-Ag levels patients were grouped in a high group separated by the median (191%).

ICG plasma disappearance rate (ICG-PDR) and ICG retention rate at 15 minutes (ICG-R15) were measured noninvasively on the day before liver resection by digital pulse densitometry using a finger piece sensor connected to a LiMON device (Pulsion Medical Systems, Munich, Germany) as described earlier.¹⁴ ICG-PDR values of >18%/min and ICG-R15 values of <10% were assumed to be normal.¹⁵

3. HVPG measurements

Portal pressure was evaluated by means of HVPG according to international standards as previously described.^{16,17} Briefly, a balloon occlusion catheter (7 F, Ferlitsch HVPG Catheter; Pejcl Medizintechnik, Austria) was placed into a large liver vein and mean HVPG was calculated from a minimum of three measurements of free and wedged hepatic vein pressures.

4. Liver resection

Liver resections were performed by an experienced team in

a two-surgeon technique using Cavitron ultrasonic surgical aspirator (CUSATM; Valleylab, Boulder, CO, USA) and bipolar forceps. Temporary inflow occlusion was applied in a minority of patients. Resections were classified according to the International Hepato-Pancreato-Biliary Association Brisbane 2000 nomenclature.¹⁸ Minor resections comprised less than three and major resections more than three Couinaud segments. Any postoperative morbidity was recorded within the first 30 days following liver resection. Morbidity was defined as any deviation from the normal postoperative course and the grade was classified according to the Clavien-Dindo classification.¹⁹

5. Histopathology

Tumor size, Edmondson and Steiner grade,²⁰ and tumor stage according to the seventh edition of the International Union Against Cancer (UICC 2009) classification of malignant tumors were assessed. Liver fibrosis was classified as proposed by Batts and Ludwig.²¹

6. Statistical analysis

Statistical analysis was performed using GraphPad Prism, version 6 (GraphPad Prism Software MedCalc Software[®], La Jolla, CA, USA). Continuous variables were reported as median and interquartile range (IQR1-IQR3) and categorical variables were reported as absolute numbers and percentages. Student t-test was used for group comparisons of continuous variables with normal distribution or with the Mann-Whitney U-test otherwise. Categorical values were compared with a chi-square test or in case of sparse data with a Fisher-exact test. Ordinal variables were tested by a chi-square trend test. Associations between continuous variables were assessed by Pearson correlation coefficients, where right-skew variables were transformed by natural logarithm to achieve normally distributed variables. As one patient has died during hospital stay, a longer hospital stay in days (concretely 130 days) was imputed for this patient in order to represent death as worst outcome (worse than any length of hospital stay). Furthermore a nonparametric Spearman correlation (r_s) was used to properly address the ordered outcome.

Survival was calculated using a Kaplan-Meier analysis and comparison was performed using a log-rank test between groups. Group differences were also described by hazard ratios (HR) and corresponding 95% confidence intervals (CI) estimated by Cox regression. Additionally, the effect of vWF on recurrence free and OS were estimated by a multiple Cox regression model to adjust for other relevant prognostic variables.

All p-values are two-sided and p<0.05 was considered statistically significant.

RESULTS

1. Patients' characteristics

Overall, 55 patients were included in this analysis. The me-

Table 1. Patient Characteristics

Characteristic	Overall (n=55)	vWF-Ag <191 (n=27)	vWF-Ag ≥191 (n=28)	p-value
Male sex	48 (87.3)	24 (88.9)	24 (85.7)	1.000
Age, yr	67.1 (62.7–71.7)	65.1 (61.6–70.1)	69.6 (63.2–74.1)	0.165
BMI, kg/m ²	28.3 (25.8–31.1)	27.3 (24.4–29)	29 (27–32.4)	0.486
Etiology of liver disease				0.695
Viral	15 (27.3)	8 (30.8)	7 (25.9)	
Non-viral	38 (69.1)	18 (69.2)	20 (74.1)	
Not determined*	2 (3.6)	1	1	
Comorbidities				
IDDM	5 (9.1)	3 (11.1)	2 (7.1)	0.670
Adipositas	14 (25.5)	5 (18.5)	9 (32.1)	0.355
NIDDM	14 (25.5)	8 (29.6)	6 (21.4)	0.547
Arterial hypertension	33 (60.0)	15 (55.6)	18 (64.3)	0.588
No comorbidities	6 (10.1)	3 (11.1)	3 (10.7)	1.000
Portal vein embolisation	8 (14.5)	4 (14.8)	4 (14.3)	1.000
ICG clearance				
PDR	17 (14.6–21.3)	19.3 (16.7–25)	15 (13.1–17.8)	0.250
R15	7.5 (4.3–13.1)	5.6 (2.5–7.9)	11 (6.3–14)	0.023
Thrombocytes, G/μL	197 (154–234)	199 (157.5–222.5)	188.5 (149.5–244.5)	0.556
α-Fetoprotein, ng/mL	5.9 (3–133.5)	9.9 (2.8–150.6)	5.7 (3.2–11)	0.706
HVPG, mm Hg	5 (4–8.25)	5 (4–5)	6 (4–10)	0.080
WHPG, mm Hg	14 (10–16)	11 (9–15)	15 (14–19)	0.017
Grade of fibrosis				0.306
0	7 (12.7)	6 (22.2)	1 (3.6)	
I	10 (18.2)	3 (11.1)	7 (25.0)	
II	8 (14.5)	5 (18.5)	3 (10.7)	
III	5 (9.1)	2 (7.4)	3 (10.7)	
IV	25 (45.5)	11 (40.7)	14 (50.0)	
Type of resection,				0.163
Major hepatectomy	20 (36.4)	7 (25.9)	13 (46.4)	
Minor hepatectomy	35 (63.6)	20 (74.1)	15 (53.6)	
Tumor size, cm	5.25 (3.25–7.75)	5.3 (3.6–6.5)	5.5 (3–11.8)	0.993
Clavien-Dindo score				0.078
I	5 (9.1)	4 (14.8)	1 (3.6)	
II	7 (12.7)	1 (3.7)	6 (21.4)	
IIIa	4 (7.3)	1 (3.7)	3 (10.7)	
IIIb	3 (5.5)	2 (7.4)	1 (3.6)	
IV	2 (3.6)	0	2 (7.1)	
V	1 (1.8)	0	1 (3.6)	
Length of stay, day [†]	10 (8–17.5)	8 (8–13.5)	11 (9–28.8)	0.008

Data are presented as number (%) or median (interquartile range).

vWF-Ag, von Willebrand factor antigen; BMI, body mass index; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-IDDM; ICG, indocyanine green; PDR, plasma disappearance rate; R15, retention rate after 15 minutes; HVPG, hepatic venous pressure gradient; WHPG, wedged hepatic venous pressure.

*Patients whose values were not determined were not included in the analysis; [†]In case of death before discharge, length of stay was imputed with 130.

dian age was 67.1 years (range, 62.7 to 71.7 years) and all patients were Child-Pugh class A (100%). The type of liver resection was minor hepatectomy in most cases (63.6%). Further baseline characteristics are shown in Table 1. Median follow-up was 20.3 months following liver resection.

2. vWF-Ag levels

Overall, the median plasma level of vWF-Ag was 191% (range, 162.5% to 277%). There was no correlation between log-HVPG and log-vWF-Ag levels measured before liver resection ($p=0.256$, $r=0.167$ based on ln-transformation of HVPG and vWF-Ag). However, we found moderate but significant correlations between log-vWF-Ag and log-tumor size (largest diameter)

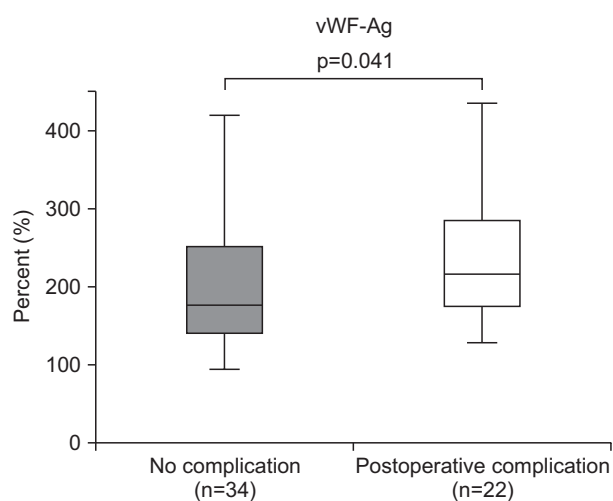


Fig. 1. von Willebrand factor antigen (vWF-Ag) levels were higher in patients with any grade of postoperative complication compared with patients without postoperative complications ($p=0.041$).

($p=0.010$, $r=0.350$ for log-transformed vWF-Ag and tumor size), wedged hepatic venous pressure ($p=0.019$, $r=0.344$) and length of stay ($p=0.0003$, $r_s=0.465$).

3. Outcome after liver resection for HCC resection

Any degree of postoperative morbidity was observed in 22 patients (40%). According to Clavien-Dindo, five patients had grade I complications (9.1%), seven patients grade II (12.7%), four patients grade IIIa (7.3%), three patients IIIb (5.5%), two patients grade IV (3.6%) and one patient suffered from a grade V complication (1.8%).

vWF-Ag levels were significantly elevated in patients who experienced any grade of postoperative morbidity (216% [178% to 283.25%] vs 176% [148% to 246%], $p=0.041$) (Fig. 1). Moreover, by using a cutoff value at the median of 191%, vWF-Ag was highly prognostic for outcome following liver resection for HCC. There was a trend towards more, and more severe surgical complications in patients with a vWF-Ag level of more than 191%. In line with this, length of stay was significantly prolonged in the latter group (8 days [range, 8 to 13.5 days] vs 11 days [range, 9 to 28.8 days], $p=0.008$) (Table 1).

Regarding long-term outcome, there was a trend towards a shorter DFS in patients with a high vWF-Ag level (median DFS, 22.8 months vs 33.4 months, $p=0.161$; HR, 1.8; 95% CI, 0.8 to 3.7) (Fig. 2A). OS was significantly diminished in patients with elevated vWF-Ag levels (median survival time, 39.8 months vs 73.4 months, $p=0.007$; HR, 4.06; 95% CI, 1.4 to 12.1) (Fig. 2B). Of note eight of 28 patients (28.6%) from the high vWF-Ag group and four of 27 (14.8%) died of HCC ($p=0.011$).

In a multivariate survival analysis differences between vWF-Ag above and below median was adjusted for other important prognostic factors (Table 2). The hazard ratio for vWF-Ag in-

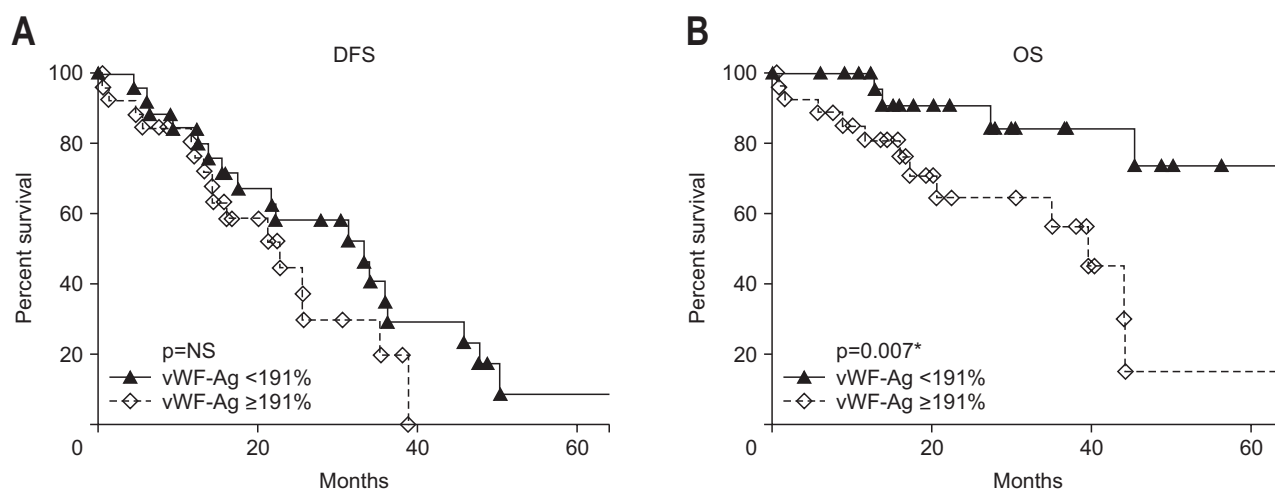


Fig. 2. Prognostic impact of preoperatively measured von Willebrand factor antigen (vWF-Ag) levels on long-term outcome after hepatectomy for hepatocellular carcinoma. (A) There was a trend towards reduced disease-free survival (DFS) in patients with a vWF-Ag level $\geq 191\%$ (median DFS, 22.8 mo vs 33.4 mo, $p=NS$). (B) Overall survival (OS) was significantly reduced in patients with elevated vWF-Ag levels (39.8 mo vs 73.4 mo, $p=0.007$).

NS, not significant. * $p<0.05$.

Table 2. Factors Influencing DFS and OS

Parameter	HR (95% CI)	p-value
DFS		
vWF-Ag*	2.31 (1.04–5.15)	0.041
Vascular infiltration [†]	1.23 (0.55–2.74)	0.613
Grade of fibrosis [‡]	0.79 (0.61–1.03)	0.080
Age, yr	0.95 (0.92–0.99)	0.005
Tumor size, cm	1.09 (1.00–1.19)	0.053
OS		
vWF-Ag*	4.89 (1.28–18.69)	0.020
Vascular infiltration [†]	0.94 (0.29–3.01)	0.919
Grade of fibrosis [‡]	0.91 (0.60–1.39)	0.663
Age, yr	1.03 (0.96–1.10)	0.436
Tumor size, cm	1.09 (0.98–1.22)	0.118

DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; vWF-Ag, von Willebrand factor antigen.

*Reference level: vWF-Ag <191%; [†]Reference level: no vascular infiltration; [‡]Grade 0 to IV.

creased for DFS (HR, 2.31; 95% CI, 1.04 to 5.15; $p=0.041$) after adjusting for effects of other covariates. Of note, patient's age (HR, 0.95; 95% CI, 0.92 to 0.99; $p=0.005$) was also significantly associated with DFS. Adjusted HR of vWF-Ag for OS also slightly increased (HR, 4.89; 95% CI, 1.28 to 18.69; $p=0.020$) (Table 2).

To test the influence of the underlying liver disease on the prediction of vWF-Ag we divided the patients according to the grade of fibrosis in low grade patients (F0-F2) and patients with fibrosis/cirrhosis (F3, F4) (Supplementary Fig. 1). Interestingly, vWF-Ag was especially predictive in patients with no or only mild signs of fibrosis in the resected specimen.

DISCUSSION

Current European Association for the Study of the Liver (EASL) guidelines base treatment allocation of patients with HCC on the Barcelona-Clinic Liver Cancer (BCLC) staging system.^{5,22,23} Resection is recommended for BCLC stages 0 and A with single tumors in case of normal bilirubin and portal pressure. Gold standard for the evaluation of portal pressure is measurement of HVPG.^{8,24,25} However, this is an invasive method and not universally available, even in specialized centers. vWF-Ag is a new, simple and noninvasive predictor of CSPH and can predict survival and decompensation in liver cirrhosis independently of MELD score. To the best of our knowledge, this is the first study that analyzed its ability to predict postoperative outcome in patients undergoing liver resection for HCC.

It has been shown that portal pressure correlates with survival after hepatectomy^{26,27} and that vWF-Ag correlates with HVPG values in patients with cirrhosis,^{28–30} thus we have speculated to find a connection between vWF-Ag levels and HVPG measured

before liver resection. Unexpectedly, we could not find any significant connection between HVPG and vWF-Ag levels in our study cohort. We assume that the lack of correlation is a result of the exclusion of patients with high HVPG levels and impaired liver function for resection.

Postoperative complications were observed in 40%, which is in range of reported rates in the literature.³¹ Patients with any grade of postoperative complication had an increased level of vWF-Ag. Inversely, patients with a vWF-Ag level of more than 191% had a trend towards more and more severe postoperative morbidity and had a significantly prolonged length of stay.

vWF not only plays a critical role in hemostasis but has been suggested to potentially promote tumor growth and dissemination.⁹ While experimental studies suggest that vWF may reduce the formation of metastases due to an anti-angiogenic and pro-apoptotic potential,⁹ clinical studies show a link between increased plasma vWF-Ag levels and worse prognosis and advanced stage in colorectal,^{32,33} gastric,¹¹ urinary bladder³⁴ and ovarian cancer.³⁵ It has been suggested that vWF may promote tumor progression, angiogenesis and metastasis formation via endothelial cell activation.^{36,37} In our study, vWF-Ag levels were significantly correlated with tumor size indicating a more advanced stage of disease. Of note, no correlation was found between tumor size and AFP. Furthermore, there was a trend towards a shorter DFS even though the observed difference did not reach statistical significance. These results suggest that vWF-Ag might also serve as a tumor marker that should be validated in future studies.

Patients with elevated vWF-Ag levels had a significantly reduced OS compared to patients with low levels. Moreover, the proportion of patients who died of HCC were doubled in patients with vWF-Ag levels of more than 191% compared to patients with lower levels, suggesting a prognostic role of vWF-Ag in oncological outcome. Whether vWF plays a causative role or just reflects an epiphenomenon of the underlying cancer-associated inflammatory process or other pathophysiological changes has not yet been elucidated.⁹

There are several limitations that need to be regarded when interpreting the results. Firstly, the study is of retrospective nature, which has a potential bias inherited to the study's design. Secondly, this analysis only includes patients with good liver function and low HVPG levels, thus assumptions to use vWF-Ag to define operability cannot be made.

To sum up, vWF-Ag is an easy to measure, valuable tool to discriminate between patients with a high risk of postoperative morbidity and an impaired long-term outcome. Further prospective trials are warranted to confirm the prognostic value of vWF-Ag and to define its role for predicting morbidity in patients undergoing liver resection in the presence of portal hypertension.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHORS CONTRIBUTIONS

Study design: M.F., A.F., M.B., K.K. Data acquisition: C.S., F.F., V.S., S.B., M.F., A.F., M.B., K.K. Data analysis: C.S., M.M., S.B., M.B., K.K. Writing of the manuscript: C.S., M.B., K.K.

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