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Prognostic Value of Preoperative Plasma Von Willebrand Factor Levels in Patients with Glioblastoma Multiforme

Seyed Reza Bagheri[1], Karim Moradian Kokhedan[2], Reza Fatahian[1]✉, Masoud Sadeghi[3]

Glioblastoma multiforme (GBM) is the most frequently occurring cancer among the primary astrocytomas. We investigated the plasma von Willebrand Factor (VWF) level and its effect on the prognosis of GBM patients. This descriptive study was conducted on 50 patients with GBM. Patient's GCS score and performance rate of each patient in one year (two 6-month periods) were recorded. The mean age of the patients was 42 years, and 56% of them were male. The mean GCS scores at baseline, after six, and twelve months were 13, 13, and 11, respectively, indicating a decreasing trend during one year. The mortality rate after six months was 14%. Most of the patients had VMF levels of 220-230 and 260-270 IU/dL. After six months based on plasma VWF level, the highest mortality happened at 290-310 and 310-320 IU/dL, and all deaths occurred at 270-350 IU/dL levels. Based on the results of this study, it can be concluded that the survival of patients with GBM reduces with increasing plasma VWF level, and this level can be effective in better clinical diagnosis and prognosis of GBM.

INTRODUCTION

Glioblastoma, formerly known as Glioblastoma multiforme (GBM), is the most frequently occurring type of cancer among the primary astrocytomas and accounts for more than 60% of all brain tumors in adults (1). GBM emanates from the glial cells and is the most invasive type of glial tumor. Based on the World Health Organization (WHO), most patients with grade IV GBM die less than a year following diagnosis (2, 3). von Willebrand Factor (VWF) is a multimeric glycoprotein that carries a coagulation pathway in the blood such as factor VIII, has a higher rate of vascular tumors, and plays an important role in determining the progression and prognosis of patients with GBM (4-6), in coagulation and mustache processes, and in angiogenesis (7). Factor VIII is one of the main coagulation factors and allows for the completion of the coagulation process (8). In order to optimize therapeutic strategies of glioblastoma, the factors influencing genetic and epigenetic prognosis have been investigated (9). Recent researches showed that genetic pathways within tumor cells may inhibit thrombotic phenomena; the prognosis becomes worse (10). VWF gene expression may be a clinically significant risk marker in lower grade glioma (11). The mutations of this gene are included methylation of the O(6)-methylguanine-DNA methyltransferase (MGMT) promoter, 1p/19q codeletion, and isocitrate dehydrogenase (IDH) 1 and 2 gene (*IDH1/2*) mutations (9,12) which provides a better responsiveness to radio- and chemotherapy (13). The clotting factor VWF is a highly adhesive procoagulant molecule that mediates platelet adhesion to endothelial and subendothelial surfaces (11). Reports have shown a direct relationship between the mentioned factor and the tumor cells and have suggested a link between the intensity of VWF staining in small vessels and astrocytes with varying degrees (4, 14, 15). If this relationship is proven in the future, it will be possible to obtain more effective therapies for this tumor by using the drugs that affect this factor. Therefore, we investigated the plasma VWF level and its effect on the prognosis of patients with GBM in the west of Iran.

[1]Department of Neurosurgery, Kermanshah University of Medical Sciences, Kermanshah, Iran; [2]Students Research Committee, Kermanshah University of Medical Sciences, Kermanshah, Iran; [3]Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran;
✉*Corresponding author*: Reza Fatahian; Department of Neurosurgery, Kermanshah University of Medical Sciences, Kermanshah, Iran. Email: rfatahian@gmail.com

MATERIALS AND METHODS

Patients

This descriptive study was approved by the Ethics Committee of Kermanshah University of Medical Sciences, Kermanshah, Iran (code: IR.KUMS.REC.1397.082). The target population included patients with GBM who were candidates for tumor resection and were admitted to the Neurological and Neurosurgical Departments of Taleghani and Imam Reza Hospitals. Informed consent was obtained from all patients. A total of 50 patients with GBM were enrolled according to the radiologist's report. For each patient, the plasma levels of VWF were monitored before surgery. After surgery, the tumor was sent to the Department of Pathology for examination. The patient's GCS score and performance rate in one year (two 6-month periods) were recorded. For this purpose, a two-part questionnaire was prepared; the first part contained the patient's demographic information and the second part was related to the

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Table 1 Characteristics of the glioblastoma multiforme patients (n=50)

Variable	Value
Age, year	
Mean ± SD (Range)	42 ± 15 (18-84)
Sex	
Male	28 (56%)
Female	22 (44%)
Job	
Self-employment	18 (36%)
Employee	13 (26%)
Housewife	11 (22%)
Student	8 (16%)
Initial GCS score	
Mean ± SD (Range)	13 ± 1 (9-15)
9	1 (2%)
10	3 (6%)
11	0 (0%)
12	6 (12%)
13	11 (22%)
14	5 (10%)
15	24 (48%)
GCS score after six months	
Mean ± SD (Range)	13 ± 1 (9-15)
9	1 (2%)
10	6 (12%)
11	2 (4%)
12	7 (14%)
13	4 (8%)
14	4 (8%)
15	26 (52%)
GCS score after one year	
Mean ± SD (Range)	11 ± 4 (3-15)
3	2 (4%)
9	2 (4%)
10	2 (4%)
11	6 (12%)
12	7 (14%)
14	6 (12%)
15	20 (40%)
Mortality after six months	
Live	43 (86%)
Dead	7 (14%)

clinical status and plasma VWF levels. After completing the questionnaire, the data were fed into SPSS software and analyzed. The relevant data were age, sex, job, VWF level, and GCS score.

Blood sample collection and VWF:Ag levels determination

Plasma was taken from each subject prior to any treatment and was poured into tubes with sodium citrate anticoagulant and centrifuged. The supernatants were stored at −70°C until the levels of VWF were assessed. VWF:Ag levels were determined using a latex particle-enhanced immunoturbidimetric assay (Instrumental Laboratory, Orangeburg, NY) that levels of 40–169 IU/dL were a normal range for O blood group and levels of 55–165 IU/dL for other blood groups (4).

Analyses

The graphs were plotted in Microsoft excel 2010. Mean (SD) and percentage were calculated by SPSS (version 22.0) software.

RESULTS

The mean age of the patients was 42 years (range: 18-84 years), 28 (56%) of whom were men (Table 1). The mean GCS scores at baseline, after six, and twelve months were 13, 13, and 11, respectively. The mean GCS score had a decreasing trend during one year. The mortality rate after six months was 14%. Figure 1 shows the frequency of the number of patients based on age group, showing most patients were in the age group 40-45 years. Figure 2 shows the frequency of the number of patients based on plasma VWF level, indicating that most patients had plasma levels of 220-230 and 260-270 IU/dL (each six patients). Figure 3 shows the frequency of the number of dead patients after six months based on plasma VWF level, showing the highest mortality rate in 290-310 and 310-320 IU/dL levels (each two-patient). All deaths occurred at 270-350 IU/dL levels.

DISCUSSION

This study evaluated the plasma VWF levels in patients with GBM in order to find its effects on the prognosis and progress of GBM. GBM is

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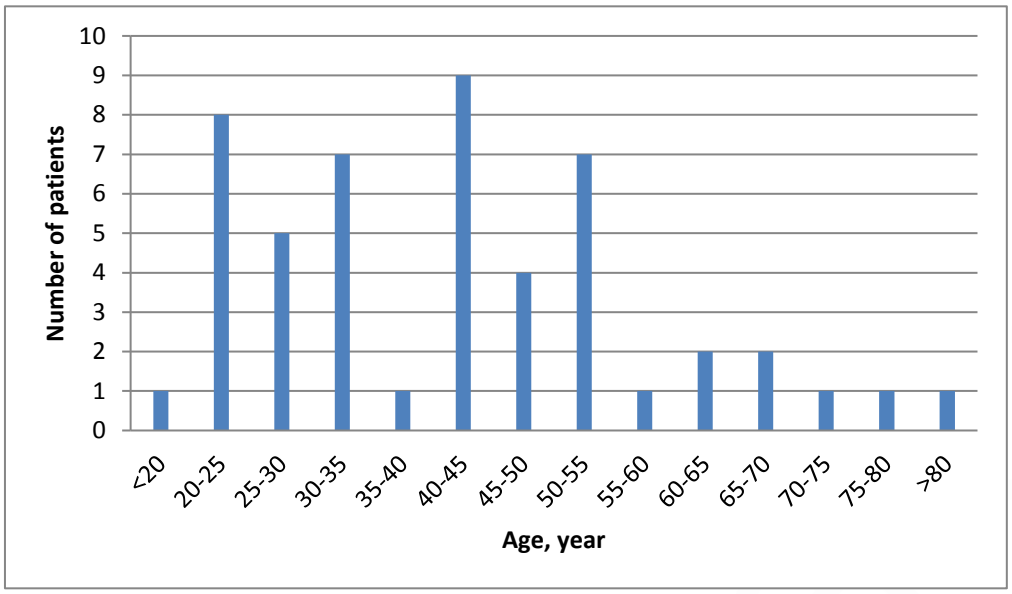

Figure 1 Frequency of number of patients based on age group

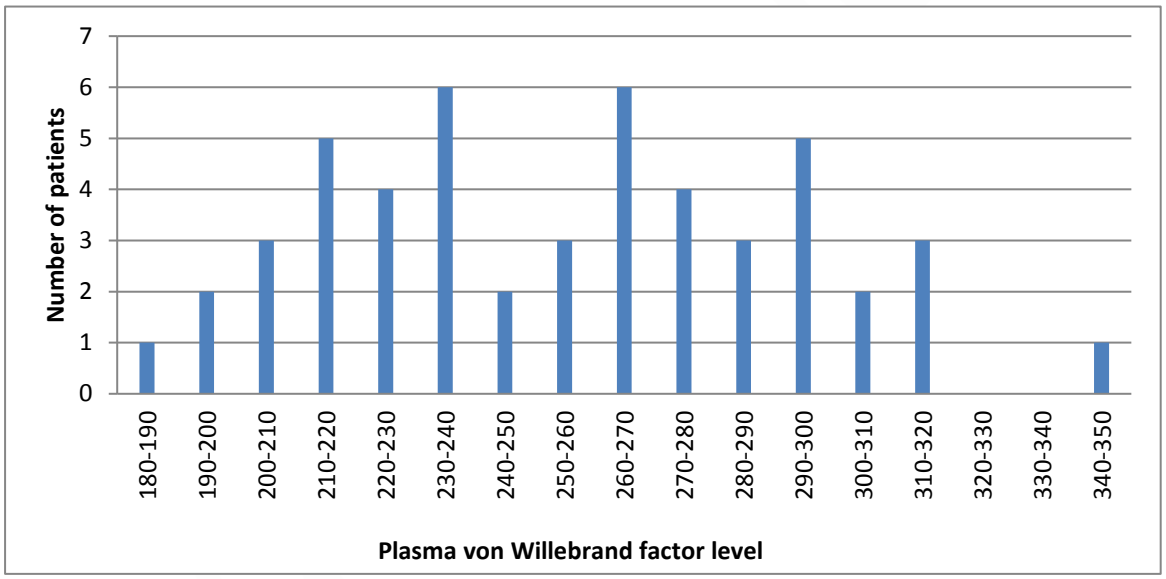

Figure 2 Frequency of the number of patients based on plasma von Willebrand factor level (IU/dL)

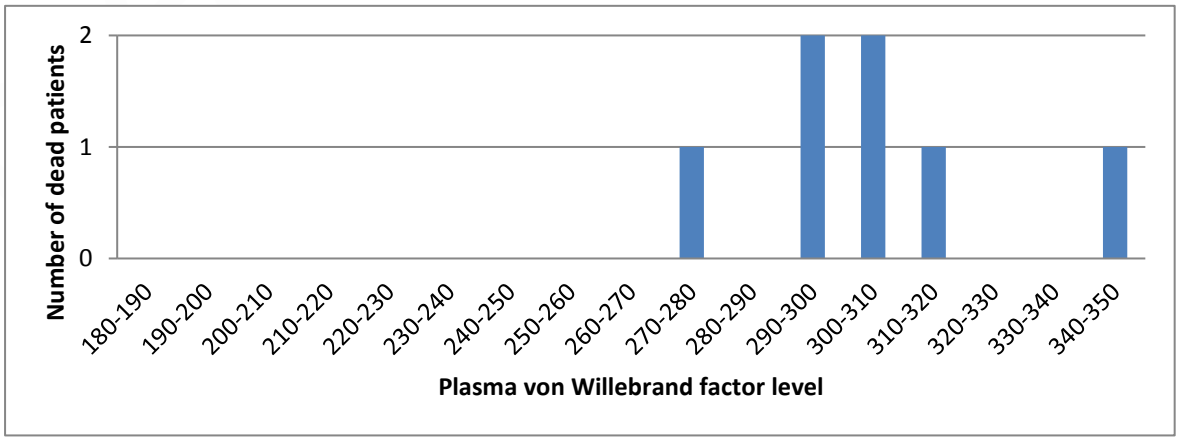

Figure 3 Frequency of the number of dead patients after six months based on plasma von Willebrand factor level (IU/dL)

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the most common malignant tumor in adults and has a poor prognosis (16). Several clinical predictors of survival have been identified such as age, preoperative functional status, and tumor size (17). In addition, some genetic and epigenetic properties can be used as prognostic factors (12). However, despite many efforts made to treat the disease, its mortality rate is very high (17, 24). Reports indicate that there is a direct relationship between the VWF and the tumor cells (18). VMF fibers promote cancer-associated platelet aggregation in the malignant melanoma of the animals and human (19), and cancer cell-derived VWF enhances gastric adenocarcinoma metastasis (20).

In the study of Marfia et al. (4), the plasma level of VWF was higher in GBM than in other gliomas. In Nierodzik's study (14), the plasma level of the above factor was significantly higher in GBM than in normal and even in grade 4 glioma tumors. In the McComb's study (5), even the endothelial cells of the small arteries of GBM produced VWF.

In the Gallinaro's study (21), GBM was commonly found in the elderly, and an increase was found in VWF level in this group of patients. VWF levels were significantly associated with survival not age. In the study of Lamszus (22), VWF in patients with GBM had a direct correlation with tumor volume and an inverse correlation with survival. In the Bhm's study (23), the VWF level in 30 patients with malignant tumors was significantly higher than those with benign tumors in the brain. One study (11) reported that lower grade gliomas with less VWF gene expression had significantly better survival than those with more VWF gene expression. Another study (4) showed that he cumulative one-year survival was significantly shorter in patients with VWF levels >200 IU/dL than in those with VWF levels <200 IU/dL, and increased VWF levels were associated with a three-fold higher risk of death in patients with GBM. The mentioned results of previous studies were consistent with the results of the present study.

CONCLUSION

Based on the results of this study, it can be concluded that survival in patients with GBM decreased with increasing plasma VWF level, and VWF level can be effective in better clinical diagnosis and prognosis of GBM. Further studies need to be done on the plasma level of VWF to monitor the therapeutic effects in a new approach to find new therapies for the disease to be used along with routine therapies.

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Conflict of interest
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