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Significance of Pretreatment Red Blood Cell Distribution Width in Patients with Newly Diagnosed Glioblastoma

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Background: Red blood cell distribution width (RDW) is a parameter of the complete blood count (CBC) test. Recent evidence suggests that pretreatment RDW is associated with patient survival in various malignant tumors. We explored the association of pretreatment RDW and other red blood cell (RBC) parameters with clinical parameters and assessed their prognostic impact on overall survival (OS) in patients with glioblastoma (GBM).

Material/Methods: In total, 109 patients with newly diagnosed GBM were retrospectively reviewed. The Cox proportional hazards regression model and Kaplan-Meier method were used to examine the survival function of pretreatment RDW, mean cell volume (MCV), hemoglobin (HGB), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC count, and hematocrit (HCT) values in patients with newly diagnosed GBM.

Results: Univariate analysis showed that MCV, MCHC, and RDW were associated with overall survival (OS). However, only RDW remained significant in multivariate analysis. The Kaplan-Meier survival curves showed that patients belonging to the high-RDW group had a worse median OS (293 days versus 375 days, P=0.023) than those belonging to the low-RDW group.

Conclusions: The present study showed that pretreatment RDW was superior to MCV and MCHC as a prognostic predictor of clinical outcome in patients newly diagnosed with GBM. Pretreatment RDW was derived directly from the CBC test, which can be easily performed in clinical practice. Therefore, pretreatment RDW values can provide additional prognostic information for patients with GBM. Further larger and prospective studies are needed to confirm these findings and to investigate the mechanism by which of RDW is associated with prognosis in patients with GBM.

MeSH Keywords: Erythrocyte Indices • Glioblastoma • Survival

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Background

Glioblastoma (GBM) is reported to account for 55.4% of all glioma cases [1]. According to the World Health Organization (WHO) classification of central nervous system tumors, GBM is the most malignant glioma and is defined as grade IV [2]. The classic treatment for GBM is maximal feasible resection combined with radiotherapy and temozolomide chemotherapy [3]. Nevertheless, survival for most patients with GBM is about 1 year, and the 5-year survival rate is only 5% [4]. Thus, it is important to explore the possible prognostic factors in patients with GBM.

Red blood cell distribution width (RDW) is a parameter of the complete blood count (CBC) test that reflects the heterogeneity of circulating red blood cell sizes [5]. It is typically used in differentiating different types of anemia. Previous studies have shown the prognostic value of RDW in patients with various cardiovascular events and other inflammatory disorders [6–9]. Recent evidence suggests that pretreatment RDW is associated with patient survival in various malignant tumors, including symptomatic multiple myeloma, esophageal carcinoma, and lung cancer [10–12]. In addition, a previous study reported that RDW was associated with patient survival in glioma, but was not an independent prognostic factor [13].

Therefore, we conducted this retrospective study on GBM, attempting to explore the correlation of pretreatment RDW and other red blood cell (RBC) parameters with clinical parameters and to assess their prognostic impact on overall survival (OS) in patients with GBM.

Material and Methods

Study population

In total, 109 patients with GBM who had undergone surgical resection at the Department of Neurosurgery, West China Hospital from June 2012 to December 2014 were included from a prospective database. All patients met the following eligibility criteria: (1) age ≥18 years; (2) patients were diagnosed by histopathology; (3) patients did not undergo previous chemotherapy and/or radiotherapy before surgery; (4) patients did not have a history of any other malignant disease; (5) patients who merely underwent tumor biopsy were excluded; (6) patients did not have a chronic inflammatory disease (including autoimmune disease and infection); and (7) the CBC tests were routinely performed within 1 week before surgery.

Data collection

Patient medical records were carefully reviewed to extract the baseline demographic and clinical data from the database, including age, sex, smoking history, tumor location, extent of tumor resection (subtotal resection or gross total resection), and adjuvant treatment (radiotherapy and chemotherapy) administered. The mean cell volume (MCV), hemoglobin (HGB), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), hematocrit (HCT), RBC count, and RDW values were obtained from the CBC tests of the patients. OS was calculated from the date of surgical resection to the time of death, or until April 2017 for patients who remained alive.

Statistical analysis

Statistical analyses to identify prognostic variables were performed using SPSS software (version 19.0). A P-value <0.05 was considered statistically significant in all analyses. The optimal cut-off values of MCV, HGB, MCH, MCHC, RBC, RDW, and HCT for predicting survival in patients with GBM were selected by use of X-tile software (Version 3.6.1, Yale University) [14]. If the X-tile software was unable to select the cut-off values of these variables, we used the cut-off value from their respective median value. The Pearson's chi-square test or continuity correction test was used to evaluate the association between categorical variables. The correlation between continuous variables was evaluated using Spearman's correlation coefficient. Univariate and multivariate statistical analyses were performed using the Cox proportional hazards regression model. Survival curves were obtained using the Kaplan-Meier method and compared by the log-rank test.

Results

Patient characteristics

The baseline characteristics of enrolled patients are shown in Table 1. Of these 109 patients, 42 (38.53%) were female and 67 (61.47%) were male. The age of the patients at the time of surgery ranged from 19 to 85 years (median age: 54 years). X-tile software was used to determine the optimal cut-off values of pretreatment RBC parameters in this study. Using the X-tile software, cut-off values of MCV, HGB, MCH, MCHC, RBC, and RDW were identified, as 94.8 fl, 121 g/l, 28.30 pg, 321 g/l, 4.29×10^{12}/l, and 14.10%, respectively (Table 1). The HCT cut-off value was selected by its median value (0.42 l/l).

The impact of pretreatment RDW and other RBC parameters on OS

At the last follow-up, 20 (18.35%) patients with GBM were still alive. Univariate analysis showed that the pretreatment RBC parameters associated with OS were MCV, MCHC, and RDW. MCV levels lower than 94.8 fl, MCHC levels greater than 321 g/l, and RDW levels lower than 14.10% were associated

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Table 1. The baseline characteristics of the enrolled patients.

Variables	N	%
Age (years)		
≥65	17	15.60
<65	92	84.40
Sex		
Male	67	61.47
Female	42	38.53
Tumor location		
Frontal lobe	46	42.20
Temporal lobe	47	43.12
Other locations	66	60.55
Extent of resection		
GTR	62	56.88
STR	47	43.12
Smoking		
Ever	22	20.18
Never	87	79.82
Adjuvant radio/chemotherapy		
Yes	76	69.72
No	33	30.28
HGB		
≥121	97	88.99
<121	12	11.01
RBC		
≥4.29	78	71.56
<4.29	31	28.44
MCV		
≥94.8	33	30.28
<94.8	76	69.72
MCH		
≥28.30	98	89.91
<28.30	11	10.09
MCHC		
≥321	82	75.23
<321	27	24.77
RDW		
≥14.10	26	23.85
<14.10	83	76.15
HCT		
≥0.42	59	54.13
<0.42	50	45.87

GTR – gross total resection; STR – subtotal resection; HGB – hemoglobin; RBC – red blood cell; MCV – mean cell volume; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; RDW – red cell distribution width; HCT – hematocrit.

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Table 2. Univariate and multivariate analyses of prognostic factors for OS of patients with glioblastoma.

Variables	Univariate			Multivariate		
	HR	95%CI	P-value	HR	95%CI	P-value
Age (years) (≥65 *vs.* <65)	2.086	1.216–3.580	0.008	2.238	1.292–3.879	0.004
Sex (Male *vs.* Female)	1.212	0.784–1.875	0.387			
Tumor location						
Frontal lobe (yes *vs.* no)	0.625	0.404–0.967	0.035	0.770	0.476–1.245	0.285
Temporal lobe (yes *vs.* no)	1.015	0.668–1.543	0.944			
Other locations (yes *vs.* no)	1.656	1.069–2.567	0.024	1.305	0.795–2.142	0.293
Smoking (ever *vs.* never)	1.277	0.769–2.123	0.345			
Extent of resection (GTR vs. STR)	0.424	0.277–0.649	<0.001	0.472	0.301–0.740	0.001
Adjuvant radio/chemotherapy (yes *vs.* no)	0.305	0.194–0.479	<0.001	0.334	0.209–0.535	<0.001
HGB (≥121 *vs.* <121)	0.578	0.307–1.089	0.090			
RBC (≥4.29 *vs.* <4.29)	0.699	0.445–1.099	0.121			
MCV (≥94.8 *vs.* <94.8)	1.615	1.037–2.516	0.034	1.331	0.827–2.139	0.239
MCH (≥28.30 *vs.* <28.30)	0.587	0.312–1.105	0.099			
MCHC (≥321 *vs.* <321)	0.577	0.362–0.920	0.021	0.668	0.407–1.095	0.109
RDW (≥14.10 *vs.* <14.10)	1.714	1.070–2.744	0.025	1.856	1.148–3.001	0.012
HCT (≥0.42 *vs.* ≥0.42)	1.116	0.732–1.703	0.609			

GTR – gross total resection; STR – subtotal resection; HGB – hemoglobin; RBC – red blood cell; MCV – mean cell volume; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; RDW – red cell distribution width; HCT – hematocrit.

with favorable OS (all P <0.05, Table 2). However, only the RDW remained significant in multivariate analysis (Table 2). Kaplan-Meier survival curves showed that patients belonging to the high-RDW group had a worse median OS (293 days versus 375 days, P=0.023, Figure 1) than those belonging to the low-RDW group.

Relationship between RDW and other RBC parameters

Different statistical methods were used to investigate the relationships between RDW and other RBC parameters. Correlations between these continuous variables were evaluated using Spearman analysis. The results showed that RDW was significantly correlated with MCV (r=–0.274, P=0.004), HGB (r=–0.254, P=0.008), MCH (r=–0.438, P<0.001), MCHC (r=–0.366, P<0.001), and HCT (r=–0.194, P=0.043), whereas RDW was not correlated with RBC (r=–0.003, P=0.972). Subsequently, the above RBC parameters were analyzed as categorical variables based on their cut-off values, and Pearson's chi-square test or the continuity correction test was used to evaluate their potential associations. The results showed that RDW (<14.10 *vs.* ≥14.10) was associated with HCT, MCH, and MCHC (all P<0.05, Table 3).

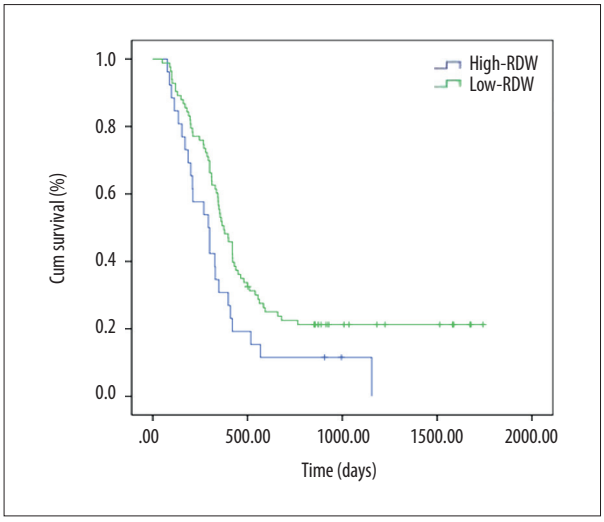

Figure 1. Kaplan-Meier analysis curve for overall survival regarding pretreatment RDW.

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Table 3. Correlations between RDW and other variables.

Variables	RDW ≥14.10	RDW <14.10	P
Age (years)			1.000**
≥65	4	13	
<65	22	70	
Sex			0.169*
Male	13	54	
Female	13	29	
Tumor location			
Frontal lobe	9	37	0.369*
Temporal lobe	10	37	0.583*
Other locations	15	51	0.733*
Smoking	4	18	0.485*
HGB			0.058**
≥121	20	77	
<121	6	6	
RBC			0.424*
≥4.29	17	61	
<4.29	9	22	
MCV			0.360*
94.8	6	27	
<94.8	20	56	
MCH			<0.001**
≥28.30	16	82	
<28.30	10	1	
MCHC			0.001*
≥321	13	69	
<321	13	14	
HCT			0.022*
≥0.42	9	50	
<0.42	17	33	

HGB – hemoglobin; RBC – red blood cell; MCV – mean cell volume; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; RDW – red cell distribution width; HCT – hematocrit; * Pearson Chi-Square test; ** continuity correction.

Discussion

In this study, our results suggested that MCV, MCHC, and RDW provide important prognostic information in patients with GBM. No previous studies have investigated the impact of MCV and MCHC on the outcomes in patients with GBM. Concerning RDW, a single study investigated its prognostic significance in patients with glioma, but it was not an independent prognostic factor [13]. In univariate analysis, MCV, MCHC, and RDW were associated with patient OS. However, in

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multivariate analysis, the prognostic value of MCV and MCHC was markedly diminished.

Previous studies identified the prognostic effect of MCV for clinical outcome in esophageal squamous cell carcinoma and lung cancer [15,16]. Results from our study showed that high MCV was closely associated with poor OS, but the exact underlying mechanism is unknown. MCV is recognized as a biomarker for internal folate concentration. Su et al. reported that when human GBM, lung cancer, and hepatocellular carcinoma cells were cultured under folate-deficient conditions, they showed a significant increase in self-renewal capability [17]. A previous report found that increased MCHC was associated with favorable outcome in lung cancer patients, which is similar to the results of our study [16]. MCHC reflects the average HGB level in an RBC. The reasons for the worse prognosis in patients with GBM with low MCHC level have not been clarified yet. As shown in Table 2, pretreatment HGB, MCH, RBC, and HCT were not correlated with the OS of patients with GBM in our study. Similarly, a previous study showed that the HGB level did not influence clinical outcome in elderly patients with GBM [18]. However, Céfaro et al. revealed that a low HGB level was associated with shorter OS in patients with high-grade gliomas [19]. Odrazka et al. identified the adverse prognostic effect of low HGB levels on the clinical outcome of GBM [20]. These discrepancies could be due to differences in the population, sample size, cut-off values, and length of follow-up.

Dagistan et al. explored the RDW levels in patients with brain tumors (including GBM), and found that the RDW was significantly higher in patients than in control subjects [21]. The potential mechanism underlying RDW involvement in tumor prognosis is poorly understood. RDW is recognized as an early indicator of increased oxidative stress, iron deficiency anemia, and iron mobilization disorders [22]. In addition, RDW elevation is markedly correlated with increase in inflammatory markers, such as soluble tumor necrosis factor receptors, interleukin-6, and C-reactive protein [23]. The results of our study suggest that pretreatment RDW is an independent prognostic factor for OS in patients with GBM. Similar findings have been obtained in studies of other malignancies. Lee et al. reported that high RDW at diagnosis was a worse prognostic factor for progression-free survival in symptomatic multiple myeloma patients [10]. Wan et al. found that high RDW was associated with poor prognosis in esophageal carcinoma patients [11]. Koma et al. reported that high values of RDW were associated with worse survival in patients with lung cancer [12]. In addition, Ay et al. demonstrated that RDW values in colon cancer patients were significantly higher than those in colon polyp patients [22].

Our study has some limitations. First, it was a retrospective, single-institution study with a small sample size. Second, we did not evaluate specific inflammatory markers such as C-reactive protein in this study because they were not routinely measured in our clinical practice. Therefore, larger prospective studies are needed to verify our findings and clarify the mechanisms underlying the association between RDW values and GBM prognosis.

Conclusions

The present study showed that pretreatment RDW was superior to MCV and MCHC as a prognostic predictor of clinical outcome in patients newly diagnosed with GBM. Pretreatment RDW was derived directly from the CBC test, which can be easily performed in clinical practice. Therefore, pretreatment RDW values can provide additional prognostic information for patients with GBM. Larger prospective studies are needed to confirm these findings and to investigate the mechanism by which RDW is associated with prognosis in patients with GBM.

Conflicts of interest

None.

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