Int J Clin Exp Med 2017;10(1):889-896
www.ijcem.com /ISSN:1940-5901/IJCEM0036263

Original Article

White blood cell count to mean platelet volume ratio (WMR) are positively correlated with disability in patients with myasthenia gravis (MG)

Zhongqian Su[1*], Zhibo Chen[1*], Bingjie Wang[2*], Dehao Yang[1], Xianfeng Lin[3], Yuanyuan Huang[1], Wenyue Liu[4], Senmin Wu[4], Qingqing Wang[5], Guoqian Chen[1], Jia Li[1], Penglei Zhu[6], Qingxuan Wang[7], Xiang Li[1], Yiyun Weng[1], Yixiang Han[8], Liangliang Ma[9], Ying Chen[1], Weiwei Xiang[1], Chenchen Zhao[10], Xu Zhang[1]

Departments of [1]Neurology, [4]Endocrinology, [6]Neurosurgery, [7]Oncological Surgery, [9]Gastrointestinal Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang, China; [2]Shanghai Children's Hospital, Shanghai Jiaotong University, Shanghai 200062, China; [3]Department of Orthopaedic Surgery, Sir Run Run Shaw Hospital, Medical College of Zhejiang University, Hangzhou 310000, China; [5]Department of Orthopaedic Surgery, The Second Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang, China; [8]Zhejiang Provincial Key Laboratory of Aging and Neurological Disease, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang, China; [10]Department of Orthopaedic Surgery, The Second Affiliated Hospital, Medical College of Zhejiang University, Hangzhou 310000, China. [*]Equal contributors and co-first authors.

Received July 20, 2016; Accepted October 30, 2016; Epub January 15, 2017; Published January 30, 2017

Abstract: White blood cell count to mean platelet volume ratio (WMR), a combination of both WBC and mean platelet volume, has been reported as a novel and promising prognostic marker in patients with non-ST elevation acute coronary syndrome and ST-segment elevation myocardial ınfarction. We speculated that WMR, a combination of two inflammatory marker (WBC and mean platelet volume), may be a novel inflammatory marker. Since the presence of inflammation plays an important role in the pathogenesis of myasthenia gravis (MG), we aimed to evaluate diagnostic information of admission WMR and the relationship between admission WMR and disease disability and progression in patients with MG. Venous blood was drawn and hematological parameters were obtained from 373 individuals comprising 185 patients with MG and 188 healthy controls (HC). We confirmed that admission WMR in MG patients were significantly higher than those in the HC group. We also found that WMR has the highest area under ROC curve (AUC 0.733, 95% CI, 0.685 to 0.778) and WMR has the highest discriminative ability for differentiating MG patients from healthy controls .Moreover, the relative increase in the mean WMR of the patients with MG were observed to be positively correlated with the degree of disease disability expressed by the MGFA clinical classification (r = 0.234, P = 0.001). Multiple regression analysis suggested that WMR was independently associated with the degree of disease disability performed by the MGFA scores after adjustment by CRP, PLR. In conclusion, we evidenced that WMR could be considered as a novel inflammatory marker in patients with MG. Furthermore, we demonstrated that WMR was positively correlated with disability in patients with MG.

Keywords: White blood cell count to mean platelet volume ratio, myasthenia gravis, disability, marker

Introduction

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction, which is clinically characterized by painless fluctuating weakness and fatigability of skeletal muscles [1]. Previous study reported that the incidence of MG varies between 1 and 2 and 5 and 15 per 100,000 population [1, 2]. As multiple factors are involved in the pathogenesis of MG, the etiology of MG remains unclear. It has been reported that the pro-inflammatory cytokines such as serum interleukin (IL)-17 levels are significantly increased and correlated with MG severity [3]. Furthermore, a multitude of literature suggests that the presence of inflammation and the regulation of immune response by cytokines play an important role in the pathogenesis of MG [4-6].

White blood cell count to mean platelet volume ratio (WMR), a combination of both white blood cell (WBC) and mean platelet volume (MPV), was defined as the ratio of absolute white blood

Table 1. MGFA clinical classification

Class I	Any ocular muscle weakness
	May have weakness of eye closure
	All other muscle strength is normal
Class II	Mild weakness affecting other than ocular muscles
	May also have ocular muscle weakness of any severity
IIa	Predominantly affecting limb, axial muscles, or both
	May also have lesser involvement of oropharyngeal muscles
IIb	Predominantly affecting oropharyngeal, respiratory muscles, or both
	May also have lesser or equal involvement of limb, axial muscles, or both
Class III	Moderate weakness affecting other than ocular muscles
	May also have ocular muscle weakness of any severity
IIIa	Predominantly affecting limb, axial muscles, or both
	May also have lesser involvement of oropharyngeal muscles
IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both
	May also have lesser or equal involvement of limb, axial muscles, or both
Class IV	Severe weakness affecting other than ocular muscles
	May also have ocular muscle weakness of any severity
IVa	Predominantly affecting limb and/or axial muscles
	May also have lesser involvement of oropharyngeal muscles
IVb	Predominantly affecting oropharyngeal, respiratory muscles, or both
	May also have lesser or equal involvement of limb, axial muscles, or both
Class V	Defined by intubation, with or without mechanical ventilation, except when used during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb

MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America.

cell count divided by mean platelet volume [7, 8]. Moreover, WMR has been reported as a novel and promising prognostic marker in patients with non-ST elevation acute coronary syndrome [7] and ST-segment elevation myocardial ınfarction [8]. White blood cell count and its subtypes are well-known to be markers of systemic inflammation. Mean platelet volume (MPV) is a potentially useful biomarker of platelet function and activity. Growing evidence indicates that MPV was correlated with inflammation process as well as disease activity in several chronic diseases such as inflammatory bowel disease (IBD) [9], rheumatoid arthritis [10]. Therefore, we speculated that WMR, a combination of two inflammatory marker (WBC and mean platelet volume), may be a novel inflammatory marker.

Since the presence of inflammation plays an important role in the pathogenesis of MG [4-6], in this study we aimed to evaluate diagnostic information of admission WMR and the relationship between admission WMR and disease disability and progression in patients with MG based on previous study.

Material and methods

We enrolled 373 individuals comprising 185 patients with myasthenia gravis (MG) and 188 healthy controls (HC) who underwent a health examination in the First Affiliated Hospital of Wenzhou Medical University, from February 2009 to March 2015. All patients with MG were hospitalized and had definite MG based on the standard clinical diagnostic criteria of Drachman [11]. In addition, the severity of MG (**Table 1**) was estimated according to the universally accepted Myasthenia Gravis Foundation of America (MGFA) clinical classification on admission [12]. The exclusion criteria were as follows: hematologic diseases, blood transfusion, other autoimmune diseases, lymphoproliferative disorders, infections, anemia as well as hepatosplenic diseases [13, 14].

Venous blood was drawn and was used for the analysis of biochemical measurements by venipuncture in the morning after an overnight fasting using a Clinical Analyzer Beckman Coulter AU5831 (Beckman Coulter, California, American). The following hematological parameters were obtained from each patient: white blood cell count (WBC), neutrophil count, lymphocyte count, platelet count, mean platelet volume (MPV), C-reaction protein (CRP). Moreover, WMR and Platelet-to-lymphocyte ratio (PLR) were calculated and the MGFA scores (given as 1-5, corresponding to I-V) was used to assess the disease disability according to the symp-

Table 2. Clinical characteristic of the subjects

	MG		HC			
	n	Result	n	Result	Reference	P
Number	185	185	188	188		
Age (Years)	185	45.59±16.83	188	47.22±14.27		0.461
Sex (F/M)	185	98/87	188	99/89		0.952
Ethnicity	185	Asian, Han	188	Asian, Han		
WBC ($\times10^9$/L)	185	6.80 (5.30, 8.99)	188	5.71 (4.65, 6.75)	4.0-10.0	<0.001
Neutrophils ($\times10^9$/L)	184	4.05 (2.90, 5.93)	188	2.99 (2.41, 3.88)	2.0-7.0	<0.001
Lymphocytes ($\times10^9$/L)	184	2.00 (1.47, 2.50)	188	2.00 (1.59, 2.40)	0.8-4.0	0.977
Platelet ($\times10^9$/L)	185	211.89±57.61	188	222.68±51.18	100-300	0.056
MPV (fl)	183	9.69±1.61	188	10.79±1.00	8.9-11.5	<0.001
PLR	184	103.97 (78.28, 139.94)	188	112.60 (86.84, 141.83)		0.244
CRP (mg/L)	40	3.46 (1.69-6.66)			0-8	

Abbreviations: MG, myasthenia gravis; HC, healthy controls; WBC, white blood cell; MPV, mean platelet volume; PLR, Platelet to lymphocyte ratio; WMR, white blood cell count to mean platelet volume ratio; CRP, C-reactive protein.

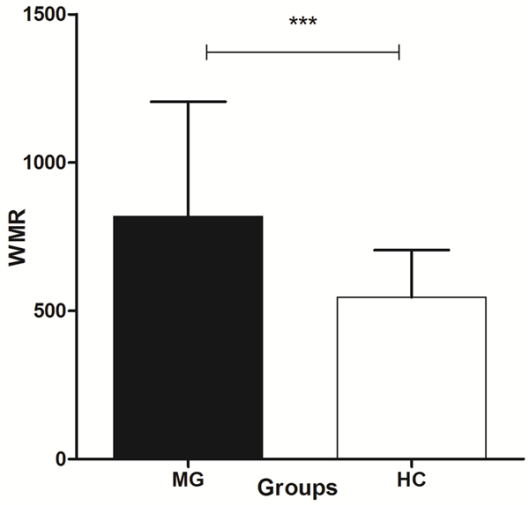

Figure 1. WMR in patients with MG and HC. MG, myasthenia gravis; HC, healthy controls. ***P<0.001.

toms and laboratory test results recorded in the medical records [15]. This study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University.

Statistical analysis

Platelet-to-lymphocyte ratio (PLR) was defined as the ratio of absolute platelet count divided by the absolute lymphocyte count and white blood cell count to mean platelet volume ratio (WMR) was defined as the ratio of absolute white blood cell count divided by mean platelet volume.

The statistical software Statistical Program for Social Sciences (version 21.0, SPSS Inc, Chicago, IL, USA) and Medcalc 11.4.2 (MedCalc Software, Mariakerke, Belgium) were used for all statistical analyses. The comparisons of the data with normal distribution between patients with MG and HC were performed using independent Student's t test. Otherwise, the Mann-Whitney U-test was used. As the data of WMR in patients with MG were continuous variables with normal distribution, WMR levels of different subgroups of patients with MG graded according to the MGFA Clinical Classification was analyzed by one-way ANOVA. The comparisons of WMR between two subgroups of patients with MG were carried out using the LSD (L) test. Enumeration data were expressed as numbers and percentiles and compared by Chi-square test. Correlations between two variables were evaluated using the Spearman approach. Besides, a multiple linear regression model was used to assess the relationship between PLR, CRP, WMR and MGFA scores. All *P* values are 2-sided and *p*-values less than 0.05 were considered statistically significant.

Results

Clinical characteristic of the subjects

Clinical features, characteristics and laboratory findings of the 185 MG patients and 188 healthy controls are presented in **Table 2**. No significant differences were observed between the two groups regarding age, gender, ethnicity, Lymphocytes, platelet, PLR. In addition, WBC and neutrophil count were increased in MG patients (P<0.001) while MPV was decreased (P<0.001).

Table 3. WMR in patients with MG

Variables	Result	T/F/Z	P
Duration of disease (years)		-1.871	0.065
≤1 (n = 129)	783.15±345.83		
>1 (n = 53)	914.10±458.88		
Age of onset (years)		-7.892	<0.001
≤50 (n = 116)	391.80±146.64		
>50 (n =68)	779.70±389.45		
MGFA		7.675	<0.001
I (n = 68)	745.64±326.53		
II (n = 56)	756.40±346.70		
III (n = 28)	799.50±371.35		
IV (n = 17)	955.72±360.73		
V (n = 14)	1288.74±529.81		
MGFA		-0.646	0.520
IIa, IIIa, IVa (n = 43)	774.99±322.83		
IIb, IIIb, IVb (n = 58)	821.85±386.24		
Thymus histology		-1.558	0.119
Nonthymoma (n = 108)	705.25 (508.44-908.70)		
Thymoma (n = 72)	833.08 (545.74-1030.79)		

WMR, white blood cell count to mean platelet volume ratio; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America.

WMR in MG patients and healthy controls

As shown in **Figure 1**, WMR in MG patients (818.24±386.67) were significantly higher than those in the HC group (545.79±159.12, P< 0.001). WMR in patients with long disease duration (>1 year) (914.10±458.88) were not significantly higher than those in patients with short disease duration (≤1 year) (783.15± 345.83, P = 0.065) (**Table 3**). Moreover, we found that WMR in patients with early-onset MG (age at onset ≤50 years) were significantly lower when compared with those in the late-onset MG (age at onset >50 years) (P<0.001) (**Table 3**). There were no significant differences between the WMR of patients with thymoma shown on MRI or computed tomography and patients without thymoma (P = 0.119) (**Table 3**). Likewise, there were no significant differences between Class IIa, IIIa, IVa (absence of bulbar involvement) and Class IIb, IIIb, IVb (presence of bulbar involvement) (P = 0.520) (**Table 3**).

WMR could differentiate MG patients from healthy controls

Cut-off values for WMR, Neutrophil, Platelet, PLR, WBC, and MPV were calculated by receiver operating characteristics curves. A WMR of 726.21 (54.10% sensitivity, 88.83% specificity, 82.50% PPV, 66.50% NPV), a Neutrophil of 4.56 (44.57% sensitivity, 88.30% specificity, 78.80% PPV, 61.90% NPV), a Platelet of 184.00 (33.51% sensitivity, 79.79% specificity, 62.00% PPV, 54.90% NPV), A PLR of 74.21 (20.65% sensitivity, 90.43% specificity, 67.90% PPV, 53.80% NPV), a WBC of 7.67 (40.54% sensitivity, 89.36% specificity, 78.90% PPV, 60.40% NPV), a MPV of 9.80 (52.46% sensitivity, 85.11% specificity, 77.40% PPV, 64.80% NPV) were found as cut-off values for differentiating MG patients from healthy controls.

WMR has the highest area under ROC curve (AUC 0.733, 95% CI, 0.685 to 0.778) and pairwise comparisons of the ROC curves revealed that WMR has the highest discriminative ability for differentiating MG patients from healthy controls (**Figure 2**; **Table 5**; Table S1).

Correlations of WMR with the clinical characteristics in MG patients

As shown in **Table 3** and **Figure 3**, the relative increase in the mean WMR of the patients with MG were positively correlated with the degree of disease disability expressed by the MGFA clinical classification (r = 0.234, P = 0.001). PLR is an inflammatory index in routine blood test and its change associate with inflammation and cytokines in several diseases such as SLE [14] and epithelial ovarian cancer [16]. Thus, in our study, PLR is also included into the multiple linear analysis. In addition, WMR positively correlated with CRP (r = 0.359, P = 0.023) (figure not shown). As WMR are influenced by CRP and other inflammatory parameters, a multiple linear analysis, including CRP, PLR and WMR, was conducted to evaluate the correlation of WMR and the MGFA scores after adjustment by other factors. WMR was associated with WBC and MPV while PLR (an accepted inflammatory marker) was associated with Platelet and Lymphocytes. Therefore we did not include WBC, Neutrophils (the biggest subtype of WBC), Lymphocytes, Platelet, MPV into the Multiple linear regression in order to eliminate

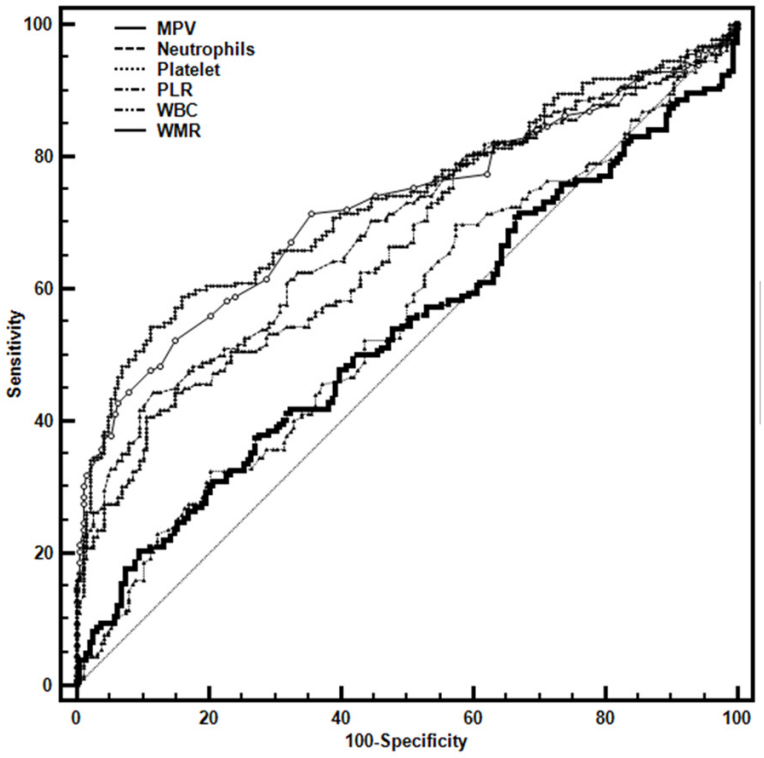

Figure 2. Receiver operating characteristic curves of WMR, Neutrophil, Platelet, PLR, WBC, and MPV for differentiating MG patients from healthy controls.

Table 4. Multiple linear regression analysis of the correlation between WMR and the MGFA scores

	Unstandardized coefficient		Standardized coefficient	P
	β	Standard error		
Constant	0.904	0.570		0.122
PLR	0.016	0.014	0.184	0.251
WMR	0.001	0.001	0.356	0.030
CRP	0.003	0.001	0.337	0.018

PLR, Platelet to lymphocyte ratio; WMR, white blood cell count to mean platelet volume ratio; CRP, C-reactive protein.

multicollinearity based on previous study [13, 14]. As shown in **Table 4**, we found that WMR was independently associated with the degree of disease disability performed by the MGFA scores after adjustment by CRP, PLR. The equation was as follows: $Y = 0.904 + 0.016X_1 + 0.001X_2 + 0.003X_3$; X_1, PLR; X_2, WMR; X_3, CRP; Y, the MGFA scores.

Discussion

In this study, we confirmed, that admission WMR in MG patients were significantly higher than those in the HC group. The cut-off value for the WMR for predicting the presence of MG was determined as 726.21 (54.10% sensitivity, 88.83% specificity). Besides, we demonstrated that there were significantly positive correlations between the WMR and CRP (r = 0.359, P = 0.023). In addition, we also found that WMR are positively correlated with disability assessed by the MGFA clinical classification in patients with MG.

As an exemplificative model for MG, experimental autoimmune myasthenia gravis (EAMG) is a B-cell mediated, T-cell-dependent autoimmune disease of the neuromuscular junction in which the nicotinic acetylcholine receptor (AChR) acts as the autoantigen [17]. Besides, it has been proposed that inflammation was triggered by complement activation at the postsynaptic muscle membrane in EAMG [18]. The Th1 cells secrete pro-inflammatory cytokines like interferon-γ (IFN-γ) and interleukin-2 (IL-2) while Th2 cells secrete anti-inflammatory cytokines such as IL-4 and IL-10. In addition, Th17 cells can secrete the novel pro-inflammatory cytokine IL-17 [19, 20] while Treg cells are also thought to be anti-inflammatory for their ability ofsuppressingcertainimmuneresponses.Furthermore, previous study demonstrated that the balance of T helper type 1 (Th1), Th2, Th17 and regulatory T (Treg) subsets of $CD4^+$ helper T cells were redistributed by upregulating Th1, Th17 subsets and downregulating Th2, Treg subsets during the development of EAMG in Lewis rats and that the interleukin-17 (IL-17) cytokine is involved in this disease [21]. There is evidence to show that monocyte play a vital role in the production of antibodies to self-AChR in the chronic phase of EAMG [22]. It is common knowledge that the circulating WBC classification undergoes relative changes under systemic inflammation and recently WBC along with its subtype counts such as Neutrophil has been identified as biomarkers of inflammation in both autoimmune and non-autoimmune diseases. Neutrophils can secrete proinflammato-

Table 5. Receiver operating characteristic curves of WMR, Neutrophil, Platelet, PLR, WBC, and MPV for differentiating MG patients from healthy controls

	MPV	Neutrophils	Platelet	PLR	WBC	WMR
AUC	0.722	0.688	0.552	0.531	0.669	0.733
SE[a]	0.0270	0.0278	0.0300	0.0303	0.0281	0.0266
95% CI[b]	0.673 to 0.767	0.639 to 0.735	0.500 to 0.603	0.479 to 0.583	0.618 to 0.716	0.685 to 0.778
cut-off value	9.80	4.56	184.00	74.21	7.67	726.21
sensitivity	52.46%	44.57%	33.51%	20.65%	40.54%	54.10%
specificity	85.11%	88.30%	79.79%	90.43%	89.36%	88.83%
NPV	64.80%	61.90%	54.90%	53.80%	60.40%	66.50%
PPV	77.40%	78.80%	62.00%	67.90%	78.90%	82.50%

[a]DeLong et al., 1988, [b]Binomial exact. AUC, area under curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

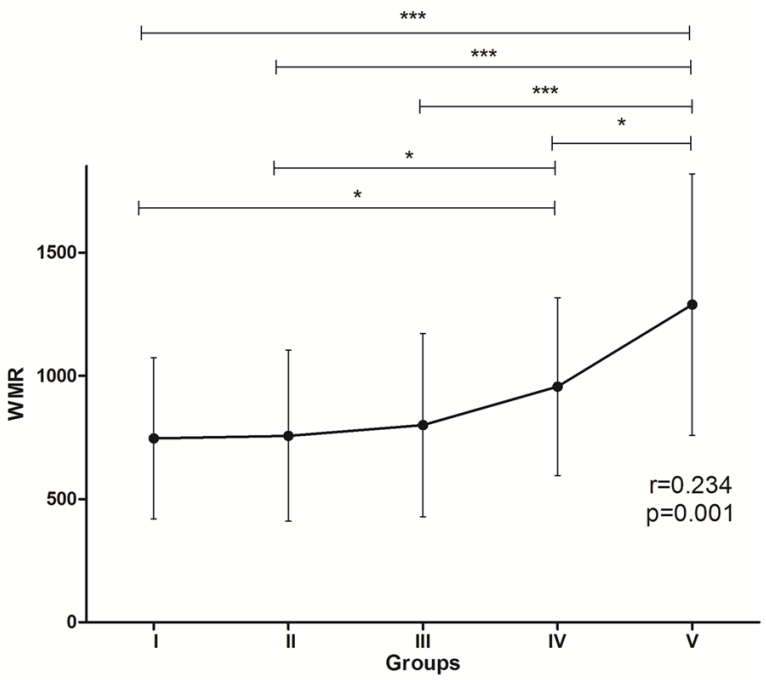

Figure 3. WMR in five subgroups of MG according to the MGFA clinical classification. MGFA, Myasthenia Gravis Foundation of America; *P<0.05, ***P<0.001.

ry enzymes, ROS and a variety of proinflammatory mediators [23]. Moreover, it has been reported that elevated numbers of pre-activated or primed neutrophils play an important role in the pathogenesis of many autoimmune diseases of the nervous system such as multiple sclerosis (MS) by elevating inflammation and tissue injury [24, 25]. As $CD4^+$ helper T cells, monocyte and Neutrophils are the subtypes of WBC, we can conclude that WBC and inflammation play a crucial role in the pathogenesis of MG.

There is evidence to demonstrate that MPV was correlated with inflammation process as well as disease activity in several chronic diseases [9, 10]. Our study showed that the WMR in patients with MG was significantly higher than those in HC. Besides, the relative increase in the mean WMR of the patients with MG were positively correlated with the degree of disease disability expressed by the MGFA clinical classification. In addition, WMR positively correlated with CRP ($r = 0.359$, $P = 0.023$). Thus, based on previous study, there is reason to speculate that WMR, as a combination of both WBC and mean platelet volume, can be considered as a new informative and Inflammatory biomarker to determine the systemic inflammatory conditions in patients with MG. WMR has been reported as a better indicator of predicting the worse outcomes in patients with NSTEMI than WBC and MPV [7]. Moreover, a previous study demonstrated that WMR is a better predictor of poor outcomes in STEMI than MPV, RDW, PLR-NLR and WBC-MPV combinations [8]. In our study, ROC curves revealed that WMR has higher area under ROC curve (AUC 0.733) and higher discriminative ability for the presence of MG than Neutrophil, WBC, Platelet, PLR, and MPV. Besides, we found that WMR are positively cor-

related with disability assessed by the MGFA clinical classification in patients with MG. Moreover, we evidenced that WMR was independently correlated with the degree of disease disability performed by the MGFA scores after adjustment by CRP, PLR in the multiple linear analysis. On the basis of these evidences, we can draw a conclusion that admission WMR is a better diagnostic marker and predictor of disease disability in MG than Neutrophil, WBC, Platelet, PLR, and MPV. Moreover, it may assist clinicians in determining patients who are more disabled and more severe. In patients with increased WMR, more effective and more intensive medical treatment may be taken into account.

There were several limitations to our study. Our research is limited to a single center due to various reasons. Besides, our study is a retrospective research and the sample size of our study was relatively small so that the results could not be absolutely conclusive in some degree. Thus, further study with more evidences is necessary to confirm our findings. In spite of these limitations, this is the first clinical study showing that WMR are positively correlated with disability as assessed by the MGFA clinical classification in patients with MG.

In conclusion, we evidenced that WMR could be considered as a novel inflammatory marker in patients with MG and that WMR possesses convenient, inexpensive and reproducible properties, which can be acquired easily from routine complete blood counts without extra cost on admission. Furthermore, we demonstrated for the first time that WMR was positively correlated with disability assessed by the MGFA clinical classification in patients with MG.

Acknowledgements

The study was financially supported by Natural Science Foundation of Zhejiang Province (No. LY13H090010) and Natural Science Foundation of Zhejiang Province (No. LQ15H090008).

Disclosure of conflict of interest

None.

Address correspondence to: Xu Zhang, Department of Neurology, The First Affiliated Hospital of Wenzhou Medical University, No. 2 Fu Xue Lane, Wenzhou 325000, Zhejiang, China. Tel: 86-152586-90163; E-mail: 15258690163@163.com; Chenchen Zhao, Department of Orthopaedic Surgery, The Second Affiliated Hospital, Medical College of Zhejiang University, Hangzhou 310000, China. Tel: 86-151577-25650; Fax: (86) 577-55579318; E-mail: 209686-5082@qq.com

References

[1] Juel VC and Massey JM. Myasthenia gravis. Orphanet J Rare Dis 2007; 2: 44.
[2] Bhandari A and Adenwalla F. Mysterious falls and a nasal voice. Lancet 2007; 370: 712.
[3] Roche JC, Capablo JL, Larrad L, Gervas-Arruga J, Ara JR, Sanchez A and Alarcia R. Increased serum interleukin-17 levels in patients with myasthenia gravis. Muscle Nerve 2011; 44: 278-280.
[4] Uzawa A, Kawaguchi N, Himuro K, Kanai T and Kuwabara S. Serum cytokine and chemokine profiles in patients with myasthenia gravis. Clin Exp Immunol 2014; 176: 232-237.
[5] Uzawa A, Kawaguchi N, Kanai T, Himuro K and Kuwabara S. Serum high mobility group box 1 is upregulated in myasthenia gravis. J Neurol Neurosurg Psychiatry 2015; 86: 695-697.
[6] Uzawa A, Kawaguchi N, Kanai T, Himuro K, Oda F and Kuwabara S. Increased serum peroxiredoxin 5 levels in myasthenia gravis. J Neuroimmunol 2015; 287: 16-18.
[7] Dehghani MR, Rezaei Y and Taghipour-Sani L. White blood cell count to mean platelet volume ratio as a novel non-invasive marker predicting long-term outcomes in patients with non-ST elevation acute coronary syndrome. Cardiol J 2015; 22: 437-445.
[8] Cicek G, Acikgoz SK, Yayla C, Kundi H and Ileri M. White blood cell count to mean platelet volume ratio: a novel and promising prognostic marker for st-segment elevation myocardial infarction. Cardiol J 2016; 23: 225-35.
[9] Kapsoritakis AN, Koukourakis MI, Sfiridaki A, Potamianos SP, Kosmadaki MG, Koutroubakis IE and Kouroumalis EA. Mean platelet volume: a useful marker of inflammatory bowel disease activity. Am J Gastroenterol 2001; 96: 776-781.
[10] Yazici S, Yazici M, Erer B, Erer B, Calik Y, Ozhan H and Ataoglu S. The platelet indices in patients with rheumatoid arthritis: mean platelet volume reflects disease activity. Platelets 2010; 21: 122-125.
[11] Drachman DB. Myasthenia gravis. N Engl J Med 1994; 330: 1797-1810.
[12] Jaretzki A 3rd, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS and Sanders DB. Myasthenia gravis: recommendations for clinical research standards. Task force of the med-

ical scientific advisory board of the myasthenia gravis foundation of America. Ann Thorac Surg 2000; 70: 327-334.
[13] Hu ZD, Sun Y, Guo J, Huang YL, Qin BD, Gao Q, Qin Q, Deng AM and Zhong RQ. Red blood cell distribution width and neutrophil/lymphocyte ratio are positively correlated with disease activity in primary Sjogren's syndrome. Clin Biochem 2014; 47: 287-290.
[14] Qin B, Ma N, Tang Q, Wei T, Yang M, Fu H, Hu Z, Liang Y, Yang Z and Zhong R. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. Mod Rheumatol 2016; 26: 372-376.
[15] Gao F, Zhao X, Zhang J, Cui X, Zhang Y, Li Q, Liu P, Fang H, Du Y, Zhang Q, Yang J and Zhang Y. Clinical features of patients with myasthenia gravis from the Henan province, China. Muscle Nerve 2016; 53: 711-716.
[16] Raungkaewmanee S, Tangjitgamol S, Manusirivithaya S, Srijaipracharoen S and Thavaramara T. Platelet to lymphocyte ratio as a prognostic factor for epithelial ovarian cancer. J Gynecol Oncol 2012; 23: 265-273.
[17] Baggi F, Annoni A, Ubiali F, Milani M, Longhi R, Scaioli W, Cornelio F, Mantegazza R and Antozzi C. Breakdown of tolerance to a self-peptide of acetylcholine receptor alpha-subunit induces experimental myasthenia gravis in rats. J Immunol 2004; 172: 2697-2703.
[18] Tuzun E, Scott BG, Goluszko E, Higgs S and Christadoss P. Genetic evidence for involvement of classical complement pathway in induction of experimental autoimmune myasthenia gravis. J Immunol 2003; 171: 3847-3854.
[19] Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, Weiner HL and Kuchroo VK. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 2006; 441: 235-238.
[20] Mangan PR, Harrington LE, O'Quinn DB, Helms WS, Bullard DC, Elson CO, Hatton RD, Wahl SM, Schoeb TR and Weaver CT. Transforming growth factor-beta induces development of the T(H)17 lineage. Nature 2006; 441: 231-234.
[21] Mu L, Sun B, Kong Q, Wang J, Wang G, Zhang S, Wang D, Liu Y, Liu Y, An H and Li H. Disequilibrium of T helper type 1, 2 and 17 cells and regulatory T cells during the development of experimental autoimmune myasthenia gravis. Immunology 2009; 128: e826-836.
[22] Kinoshita I, Nakamura T, Satoh A, Matsuo H, Seto M, Tomita I, Tsujihata M and Nagataki S. Role of the macrophage in the pathogenesis of experimental autoimmune myasthenia gravis. J Neurol Sci 1988; 87: 49-59.
[23] Demirci S, Demirci S, Kutluhan S, Koyuncuoglu HR and Yurekli VA. The clinical significance of the neutrophil-to-lymphocyte ratio in multiple sclerosis. Int J Neurosci 2016; 126: 700-706.
[24] Steinbach K, Piedavent M, Bauer S, Neumann JT and Friese MA. Neutrophils amplify autoimmune central nervous system infiltrates by maturing local APCs. J Immunol 2013; 191: 4531-4539.
[25] Tillack K, Naegele M, Haueis C, Schippling S, Wandinger KP, Martin R and Sospedra M. Gender differences in circulating levels of neutrophil extracellular traps in serum of multiple sclerosis patients. J Neuroimmunol 2013; 261: 108-119.

Table S1. Pairwise comparison of ROC curves

WMR~MPV	
Difference between areas	0.0117
Standard Error[c]	0.0267
95% Confidence Interval	-0.0406 to 0.0641
z statistic	0.440
Significance level	P = 0.6600
WMR~Neutrophils	
Difference between areas	0.0450
Standard Error[c]	0.0165
95% Confidence Interval	0.0126 to 0.0773
z statistic	2.725
Significance level	P = 0.0064
WMR~Platelet	
Difference between areas	0.182
Standard Error[c]	0.0464
95% Confidence Interval	0.0907 to 0.273
z statistic	3.915
Significance level	P = 0.0001
WMR~PLR	
Difference between areas	0.202
Standard Error[c]	0.0362
95% Confidence Interval	0.131 to 0.273
z statistic	5.585
Significance level	P<0.0001
WMR~WBC	
Difference between areas	0.0649
Standard Error[c]	0.0124
95% Confidence Interval	0.0406 to 0.0892
z statistic	5.236
Significance level	P<0.0001

[c]DeLong et al., 1988.