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Comparative Study of the Clinical Application of 2 Bleeding Grading Systems for Pregnant Women With Immune Thrombocytopenia

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Abstract

Objective: To compare the clinical practicability of two bleeding grading systems (BGS) in pregnancy with Immune Thrombocytopenia (ITP). **Methods:** The clinical data of 154 cases were retrospectively analyzed with the 2016 version of the ITP Bleeding Scale (ITP-2016) and the ITP-specific bleeding assessment tool (ITP-BAT). The correlation between the two BGS and the relations among the platelet counts, gestational ages, and disease stages were respectively analyzed. **Results:** There is no significant difference between the two BGS in the patients' ages, nor between the newly diagnosed and the persistent group or the chronic group, while the difference between the persistent and the chronic group was significant ($P = 0.001$; $P = 0.001$). There is a negative correlation between the bleeding grade and platelet count ($r = -0.436$; $r = -0.390$), while the correlation between the two BGS was positive ($r = 0.921$). The proportions of identical scores provided by two different physicians using the two BGS were 94.8% and 93.5%. The difference before and after the treatment were significantly different ($P = 0.013$; $P = 0.037$). It takes less time to score with the ITP-2016 ($P = 0.011$). **Conclusion:** Both systems can be useful for disease evaluations, risk assessments and efficacy evaluations in Chinese pregnant women with ITP. The ITP-2016 takes less time and is more suitable for Chinese pregnant patients with ITP.

Keywords

ITP, pregnancy, bleeding grade, platelet count

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Introduction

Immune thrombocytopenia (ITP) is more common in women, especially during childbearing ages.[1,2] The severity of bleeding is usually not consistent with the platelet (PLT) count. At present, it is believed that the timing of treatments and the choice of treatment plan for pregnancy with ITP depend on the PLT count and bleeding manifestations. It can either cause overtreatment or delay the optimal treatment. The ITP International Working Group (IWG) recommended the use of ITP-specific bleeding assessment tool (ITP-BAT) in evaluating the risk of bleeding,[3] but its clinical application was limited due to the long-term data collection. In order to shorten the evaluation time and improve the clinical operability, the 2016 version of ITP Bleeding Score Scale (ITP-2016) was recommended by Chinese specialists to be used in adult ITP.[4] This study retrospectively analyzed the clinical data of pregnant women with ITP to compare the clinical practicability of these 2 bleeding grading systems (BGS) in Chinese patients with ITP and pregnancy.

Patients and Methods

Patient Population

This retrospective study collected the clinical data of 154 cases of pregnant patients with ITP admitted to the Department of Hematology, Fujian Institute of Hematology, Fujian

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Table 1. 2016 Version of the ITP Bleeding Grading System (ITP-2016).

	Age (Year)		Subcutaneous Hemorrhage (Petechiae/Ecchymosis/ Hematoma)		Mucosal Hemorrhage (Nasal Cavity/Gums/ Oral Mucosa/Bloody Bulla/Conjunctive)			Visceral (Internal Organs) Hemorrhage (Lung, Gastrointestinal Tract, Urogenital System)			
Score	≥65	≥75	Head and Face	Other Parts	Sporadic, Automatic cease	Frequent, Hard to Cease	With Anemia	Without Anemia	With Anemia	Life Threatening	CNS
1	√			√							
2		√	√		√						
3						√		√			
5							√		√		
8										√	√

Abbreviations: CNS, central nervous system; ITP, immune thrombocytopenia.

Provincial Key Laboratory on Hematology, and Fujian Medical University Union Hospital in Fuzhou, Fujian Province, China between April 2013 and July 2018. The inclusion criteria were as follows: (1) pregnancy without other complications, (2) compliance with the diagnostic criteria of ITP, and (3) first PTL count of $<70 \times 10^9$/L within 28 weeks of pregnancy.[5] The patients were divided into the following groups: newly diagnosed ITP (within 3 months of diagnosis of ITP), persistent ITP (3-12 months of PLT reduction after diagnosis of ITP), and chronic ITP (more than 12 months of PLT reduction).[6] The ITP-2016 (Table 1) and ITP-BAT were used to evaluate bleeding. The relationship between the 2 BGS and the patient's age, PLT count, and disease phase were analyzed, as well as the correlation and consistency of the 2 BGS. In addition, 82 patients receiving glucocorticoid and/or intravenous immunoglobulin therapy were scored by the 2 BGS before and after the treatments, and the treatment effects were evaluated according to the score and PLT count results.

2016 Version of the ITP Bleeding Scoring System (ITP-2016)

The bleeding score is calculated by the sum of the age score and bleeding manifestation score (the highest score among all the bleeding scores), as shown in Table 1.[4]

Immune Thrombocytopenia–Specific Bleeding Assessment Tool

The bleeding symptoms are grouped into 3 major domains: skin (S), visible mucosae (M), and organ (and internal mucosae) (O).[3] In accordance with the WHO bleeding scoring criteria, the severity of bleeding was graded by the SMO scoring system: severe bleeding (affecting vital signs): O (>3); massive bleeding: M (>3); moderate bleeding: S = 3, M = 2, O = 2; mild bleeding: S < 3, M = I, O = 1; and no bleeding: S = 0, M = 0, O = 0. Rodeghiero et al defined S > 3, M > 1, and O > L as hemorrhages of clinical significance. The IWG does not recommend defining bleeding by summing the SMO scores. However, in this study, to verify the consistency of the ITP-BAT score with the ITP-2016 score, we compared the average SMO total score with the ITP-2016 score.

The score is composed of an age score and a bleeding score. Patients aged older than 65 years are assigned 1 point, and ≥75years are assigned 2 points. Bleeding manifestations are grouped into 3 major domains: skin, mucosa, and internal organs. Each domain is further divided into different scoring items as follows: (1) skin hemorrhages, including petechiae, purpura, ecchymosis, and hematomas (head and face, 2 points and other parts, 1 point); (2) mucosal hemorrhages, such as bleeding from the nasal cavity, gums, oral mucosa, or conjunctiva (sporadic and automatic cease, 2 points; frequent and hard to cease, 3 points; and with anemia, 5 points); and (3) internal organ hemorrhages, including bleeding from a lung, the gastrointestinal tract, the urogenital tract (without anemia, 3 points; with anemia, 5 points; and life-threatening, 8 points), or the central nervous system (CNS, 8 points).

Efficacy of the ITP-2016 and ITP-BAT in Evaluating the Treatment Effects

A total of 82 patients receiving glucocorticoid and/or intravenous immunoglobulin therapy were scored by the 2 BGS before and after the treatments, and the treatment effects were evaluated according to the bleeding scores and PLT count.

Statistical Analyses

SPSS22.0 statistical software was used to analyze the data, and a single sample K-S test was used to test the normality of the data. If the quantitative data followed a normal distribution, the data were described by the mean ± standard deviation ($x \pm s$); otherwise, the data were described by the median (M) and interquartile ranges. If the paired design data between 2 groups followed a normal distribution, a paired sample t test was used; otherwise, a paired design Wilcoxon test, a nonparametric test, was used. The correlation between the bleeding score and PTL count was analyzed by Spearman rank-order correlation. The value of the bleeding score was $-1 < R < 1$, $r > 0$ indicated a

Table 2. Data of 154 Pregnancies With ITP and the ITP-2016 Scores.

Index	Score 0 (n = 67)	Score 1 (n = 4)	Score 2 (n = 19)	Score 3 (n = 33)	Score 5 (n = 31)
Newly diagnosed	5 (7.50)	0 (0.0)	3 (15.8)	5 (15.2)	1 (3.20)
Persistent ITP	42 (62.7)	1 (25.0)	8 (42.1)	7 (21.2)	13 (41.9)
Chronic ITP	20 (29.8)	3 (75.0)	8 (42.1)	21 (63.6)	17 (54.9)
PLT count ($\times 10^9$/L)	57 (36-80)	52 (32.5-88.75)	60 (39-77)	40 (24.5-60)	30 (14-52)

Abbreviations: ITP, immune thrombocytopenia; ITP-BAT, immune thrombocytopenia–specific bleeding assessment tool; PLT, platelet.

Table 3. Data of 154 Pregnancies With ITP and the ITP-BAT Scores.

Index	No Bleeding (n = 67)	Mild Bleeding (n = 27)	Moderate Bleeding (n = 36)	Massive Bleeding (n = 19)	Severe Bleeding (n = 5)
Newly diagnosed	5	4	4	1	0
Persistent ITP	42	9	14	5	0
Chronic ITP	20	14	18	13	5
PLT count ($\times 10^9$/L)	57 (36-80)	40 (20-65)	32.5 (21.3-60)	40 (15-60)	45 (14.5-71)

Abbreviations: ITP, immune thrombocytopenia; ITP-BAT, immune thrombocytopenia–specific bleeding assessment tool; PLT, platelet.

positive correlation, and $r < 0$ indicated a negative correlation. A χ^2 test was used to test the difference between the 2 BGS at different disease phases. The Bonferroni correction method was used for the comparisons between the 2 groups of multiple samples. The Kruskal-Wallis test was used to examine the difference between the 2 groups of bleeding scores at different gestational ages. The κ test was used to analyze the consistency of the 2 scores: $K > 0.75$ indicated good consistency, $0.4 < K < 0.75$ indicated moderate consistency, and $K < 0.4$ indicated poor consistency. The changes in the bleeding score and PTL count before and after the treatments were examined by a paired Wilcoxon test. $P < .05$ was statistically significant.

Results

Clinical Characteristics of the Patients

A total of 154 patients' data were collected. Among these patients, there were 14 newly diagnosed cases, 71 persistent cases, and 69 chronic cases. Sixty-seven (43.5%) patients had no symptoms of bleeding; of the 87 (56.5%) patients who had symptoms of bleeding, 31 patients had hemorrhages accompanied by anemia, and no patients had life-threatening hemorrhages.

Immune Thrombocytopenia-2016/ITP-BAT Scoring of These Patients

One hundred fifty-four patients were scored by the ITP-2016, of which 67, 4, 19, 33, and 31 had scores of 0, 1, 2, 3, and 5, respectively (Table 2). They were also scored by the ITP-BAT, of which 67, 27, 36, 19, and 5 were considered to have no bleeding, mild bleeding, moderate bleeding, massive bleeding, and severe bleeding, respectively (Table 3).

Table 4. The Relationship Between the Scores and Disease Stages.

Index	Nonbleeding (n)	Bleeding (n)	Bleeding Rate (%)	χ^2	*P* Value
Newly diagnosed					
ITP-2016	5	9	64.3	13.340	.001
ITP-BAT	5	9	64.3	14.446	.001
Persistent ITP					
ITP-2016	42	29	40.8		
ITP-BAT	42	28	40.8		
Chronic ITP					
ITP-2016	20	49	71.0		
ITP-BAT	20	50	71.0		

Abbreviations: ITP, immune thrombocytopenia; ITP-BAT, immune thrombocytopenia–specific bleeding assessment tool.

Correlation Analysis of the ITP-2016 Score With Patients Age, Disease Phase, and PLT Count

There was no significant difference among pregnant women of different age groups in the ITP-2016 score ($\chi^2 = 2.463$, $P = .651$). There were significant differences in the scores individuals with different disease phase ($\chi^2 = 13.340$, $P = .001$; Table 4). Bonferroni calibration was used to compare the bleeding rates between groups. The results showed that there was a significant difference in the bleeding rates between persistent ITP and chronic ITP ($P = .001$). No significant difference in bleeding rates was found between newly diagnosed ITP and persistent/chronic ITP ($P = .431$, $P = 1$), but the bleeding rate of chronic cases was higher than that of persistent cases. The ITP-2016 score was negatively correlated with the PLT count ($r = -0.436$, $P < .001$), which means that the lower the PLT count was, the higher the bleeding score.

Table 5. Changes in the PLT Count and Corresponding Bleeding Score in Patients Before and After the Treatments.

Index	Case	Before Treatment	After Treatment	*Z*	*P* Value
PLT count ($\times 10^9$/L)	82	15 (7.75-24.0)	66 (46.75-88.75)	−7.781	<.001
ITP-2016 score	82	2.5 (0-3)	0 (0-3)	−2.497	.013
ITP-BAT score	82	1.0 (0-1.3)	0 (0-1.3)	−2.082	.037

Abbreviations: ITP, immune thrombocytopenia; ITP-BAT, immune thrombocytopenia–specific bleeding assessment tool; PLT, platelet.

Correlation Analysis of ITP-BAT Score With Patients Age, Disease Phase, and PLT Count

There was no significant difference in the ITP-BAT scores among pregnant women of different age groups ($\chi^2 = 4.455$, $P = .108$), but there were significant differences in the scores of individuals with different disease phase ($\chi^2 = 14.446$, $P = .001$; Table 4). A significant difference in the bleeding rates was found between persistent ITP and chronic ITP ($P = .001$), while there was no significant difference in bleeding rates between newly diagnosed ITP and persistent/chronic ITP ($P = .420$, $P = 1$). There was no difference in the bleeding rate between newly diagnosed cases and persistent/chronic cases, but the bleeding rate of patients with chronic cases was higher than that of patients with persistent cases. The ITP-BAT score was also negatively correlated with the PLT count ($r = -.436$, $P < .001$).

Correlation Analysis of the ITP-2016 and ITP-BAT

The ITP-BAT score was positively correlated with the ITP-2016 score ($r = 0.921$, $P < .001$).

Consistency Analysis of the ITP-2016 and ITP-BAT in Hematologists and Obstetricians

These patients were randomly scored by hematologists and obstetricians by the 2 BGS at the same time. When the ITP-BAT was used, the coincidence rate between the scores from the hematologists and obstetricians was 93.5% ($K = 0.868$, $P < .001$). When scored with the ITP-2016, the coincidence rate between the scores from the hematologists and obstetricians was 94.8% ($K = 0.894$, $P < .001$).

Comparisons of the Time Spent on the ITP-2016 and ITP-BAT

There was a significant difference in the time required to score between the ITP-2016 and the ITP-BAT ($Z = -2.546$, $P = .011$). The ITP-2016 takes less time than the ITP-BAT (1.5 [1-2] minutes vs 3 [2-6.25] minutes).

Analysis of the Efficacy of the ITP-2016

Before the treatments, the 82 patients who received glucocorticoid or (and) intravenous immunoglobulin were evaluated by the ITP-2016. The 0-, 1-, 2-, 3-, and 5-point groups included 33 (40.2%) cases, 2 (2.5%) cases, 6 (7.3%) cases, 23 (28.1%) cases, and 18 (21.9%) cases, respectively. These patients were reevaluated by the ITP-2016 after the treatments. The 0-, 1-, 2-, 3-, and 5-point groups included 49 (59.8%) cases, 0 (0%) cases, 0 (0%) cases, 25 (30.5%) cases, and 8 (9.7%) cases, respectively. The PLT count increased after the treatments, and it was significantly different after the treatments compared with before treatments ($Z = -7.781$, $P < .001$). The results of the bleeding assessment before and after the treatments were also statistically significantly different ($Z = -2.497$, $P = .013$; Table 5).

Analysis of the Efficacy of the ITP-BAT

These 82 patients were also evaluated by the ITP-BAT. The no bleeding, mild bleeding, moderate bleeding, massive bleeding, and severe bleeding groups included 33 (40.2%) cases, 37 (45.1%) cases, 12 (14.6%) cases, 0 (0%) cases, and 0 (0%) cases, respectively. After treatment, these patients were reevaluated by the ITP-BAT. The no bleeding, mild bleeding, moderate bleeding, massive bleeding, and severe bleeding groups included 50 (61.0%) cases, 0 (0%) cases, 8 (9.8%) cases, 19 (23.1%) cases, and 5 (6.1%) cases, respectively. There were significant differences in the ITP-BAT scores before and after the treatments ($Z = -2.082$, $P = .037$; Table 5).

Discussion

Thrombocytopenia occurs in 5% to 10% of women during pregnancy or immediately after delivery. Although ITP accounts for only 3% of all causes of thrombocytopenia during pregnancy, it is the most common cause of thrombocytopenia in patients with PLT counts lower than 50×10^9/L in the early and middle pregnancy periods.[1] Pregnancy can aggravate thrombocytopenia and lead to an increase in perinatal maternal and neonatal mortality. The clinical manifestations of the disease include short-term or a continuous decrease in PLT count, a spontaneous or scratched hemorrhage and purpura in mucosa and subcutaneous tissue. Intracranial hemorrhages are rare.[7] Patients with PLT counts $<20 \times 10^9$/L are at risk of a spontaneous hemorrhage, a postpartum hemorrhage, and placental abruption. Disseminated intravascular coagulation may occur in severe cases, which poses a threat both to maternal and to fetal health.[8] In this study, 154 cases of pregnancy with ITP were mainly manifested by skin mucosa, gingiva, and epistaxis. None of them had life-threatening hemorrhages, which are consistent with the results in the relevant literature. In the past, the assessment of the condition, the evaluation of the risk of

bleeding, and the curative effect mainly depend on the PLT count. But in some patients, the severity of bleeding is not consistent with the decrease in the PLT count. Patients with a low PLT count may not have bleeding manifestations, and the probability of secondary fatal or CNS bleeding is also quite low. Blindly pursuing an increase in PLT count is bound to require long-term maintenance of drug use, resulting in unnecessary drug toxicity, side effects, and increased costs.

In recent years, several BGS for assessing the risk of bleeding in patients with ITP have been used to guide clinicians in selecting treatment options and evaluating the implication of the PLT counts, but they have not been widely used in clinics.[9,10] The IWG has recommended the use of the ITP-BAT. The hemorrhage score was not related to the patient's age, sex, or disease phase but was negatively correlated with the PLT count. The difference in the ITP-BAT hemorrhage score and PLT count before and after the treatments was statistically significant. The consistency of the 2 individual physicians' scores was 66.1%.[11] Therefore, this evaluation tool has been widely used in the international community to quantify the bleeding condition of patients with ITP. However, its practicability in clinical applications is limited because it is complex and time-consuming.

The ITP-2016 has been recommended by the Society of Hematology, Chinese Medical Association.[4] It has the characteristics of simplicity and improves its clinical practicability. Xiao et al evaluated the clinical value of the ITP-2016 in adult patients with ITP.[11] The results showed that the hemorrhage score was not related to sex or disease phase but was negatively related to PLT count. There were significant differences in the PLT count and bleeding score before and after the treatments. The consistency of the 2 individual physicians' scores was 94.4% and that of the same physician's 2 scores was 94.7%. Compared with the ITP-BAT scoring system, the ITP-2016 takes less time to score.

But it is unclear whether they are useful in pregnant women with ITP or not. In this study, the ITP-2016 and ITP-BAT scoring systems were used to score the 154 pregnant patients with ITP. The results showed that there were a positive correlation and good consistency between the 2 bleeding scoring systems. The 2 bleeding scores were negatively correlated with the PLT count. There was a correlation between the scores and the different disease phase. There was a significant difference in the scores between persistent ITP and chronic patients with ITP, which were both different from the scores of nonpregnant patients with ITP. One possible reason for this difference may be that the autoantigens caused by the changes in PLT structural antigens shorten the PTL life span in pregnant women with persistent/chronic ITP. Another reason may be that it is related to the physiological changes in women during pregnancy, which lead to a relative decrease in the PLT count.

At least 15% to 35% of pregnant women with thrombocytopenia require treatments, even prior to symptoms of pain and delivery.[12-14] The 2011 ASH guidelines and the 2016 Edition of the Consensus among Chinese Experts recommend glucocorticoids and intravenous immunoglobulin as the first-line drugs for ITP treatment.[4] We used the ITP-2016 and ITP-BAT scoring systems to score 82 patients who received glucocorticoid and/or intravenous immunoglobulin before and after the treatments and found that the PLT count increased and the risk of bleeding decreased significantly after the treatments compared with before the treatments. The ITP-2016 and ITP-BAT scores were consistent, and both scores had a good response to the treatment of patients with ITP. Doctors of different specialities have good consistency in the clinical application of these 2 scoring systems in pregnant patients with ITP, indicating that these 2 scoring systems can be used as effective tools for patient condition evaluations, risk assessments, and curative effect evaluations. The indexes in the ITP-2016 are concise, so it is easier to understand and less time-consuming than the ITP-BAT scoring system. Therefore, the ITP-2016 is conducive to evaluate the bleeding risk of Chinese pregnant patients with ITP in hospitals of all levels or multicenter clinical trials.

Authors' Note

Our institution does not require ethical approval for reporting individual cases or case series. Verbal informed consent was obtained from the patients for their anonymized information to be published in this article.

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