**CLINICAL RESEARCH** 

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Received: 2020.09.15 Accepted: 2020.11.09 ble online: 2020.12.09 Published: 2021.02.13		Factors Affecting the Ris Hemorrhage in Pregnan Facilities	sk of Postpartum t Women in Tibet Health
Authors' Contribution: Study Design A Data Collection B Statistical Analysis C Data Interpretation D Manuscript Preparation E Literature Search F Funds Collection G	BCE CF DF DF F CF F AE	Zhuo-Ma Pubu Zhuo-Ma Bianba Ge Yang La-Mu CyRen De-Ji Pubu Ka-Zhu Suo Lang Bian Zhen Qu-Zong Zhaxi Zhuo-Ga Nyma	Department of Obstetrics and Gynecology, Lhasa People's Hospital, Lhasa, Tibet, P.R. China
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Bacl Material/A	kground: Aethods: Results:	Postpartum hemorrhage (PPH), the leading cause of n 24 h after vaginal delivery or >1000 mL within 24 h af incidence of PPH and assess its risk factors in pregnar this region. A total of 4796 pregnant women with gestational age tween December 2010 and December 2016 were inv and pregnancy outcomes were collected. The related tivariable logistic regression. The area under the curve to evaluate the effect of the PPH prediction model. PPH occurred in 95 women, with an incidence of 1.98°	naternal death, is defined as a blood loss >500 mL within fter cesarean section. This study aimed to investigate the nt women in Tibet to provide a reference for clinicians in $e \ge 28$ weeks who were admitted to hospitals in Tibet be- volved in this study. Patient sociological and clinical data risk factors of PPH were analyzed by univariate and mul- e of the receiver operating characteristic curves was used %. The following factors were associated with higher risk
Con	clusions:	for PPH: maternal age $\geq$ 35 (odds ratio [OR]=1.96; 95% preterm birth (OR=2.66; 95% Cl, 1.60-4.42; P<0.001), of neonatal weight >4 kg (OR=3.92; 95% Cl, 1.75-8.81; P 95% Cl, 2.22-13.74; P<0.001). Maternal age $\geq$ 35, history of preterm birth, cesarean were risk factors of PPH, which can help evaluate PPF	% confidence interval [CI], 1.18-3.27; $P$ =0.010), history of cesarean section (OR=6.69; 95% CI, 4.30-10.40; $P$ <0.001), P<0.001) and occurrence of neonatal asphyxia (OR=5.52; n section, newborn weight >4 kg, and neonatal asphyxia H in Tibet.
Ke	ywords:	Delivery, Obstetric • Postpartum Hemorrhage • Pr	regnant Women • Risk Factors
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# Background

Postpartum hemorrhage (PPH) is defined as a loss of blood >500 mL within 24 h after vaginal delivery or > 1000 mL blood loss within 24 h after cesarean section. PPH remains a serious problem in pregnant women worldwide. Tibet is located in the Qinghai-Tibet Plateau and has an average altitude of more than 3000 meters above sea level. Low pressure and low oxygen decrease artery oxygen saturation. The incidence of PPH in pregnant women in the plateau is 2 to 7 times higher than that in plain areas [1]. As an obstetric emergency, PPH can cause sequelae such as hypotension, anemia, and fatigue, affecting puerperal recovery and even endangering the life of the puerpera in severe cases [2]. A previous study reported that PPH occurs in 18% of deliveries, which causes huge loss of life and property in society [3]. PPH is one of the major causes of maternal morbidity and mortality, despite major improvements in biomedicine and reproductive health services [4,5]. Recently, several studies have indicated that PPH results in 26.7% of severe adverse maternal outcomes and 29.3% of maternal deaths globally [6-8]; it is one of the main contributors to maternal death in the world and in China [9]. Therefore, giving attention to PPH is crucial for improving pregnancy outcomes.

The occurrence of PPH is influenced by various factors, including adherent placenta, uterine atony, genital tract injury, and coagulopathy [10-13]. Although obstetricians have taken some measures such as administering oxytocin during childbirth, the incidence of PPH remains high [14]. Fukami et al believe that regardless of the clinical etiology, the high incidence of PPH may result from characteristics of the maternal population [10]. Previous studies revealed that PPH history, multiple pregnancies, macrosomia, primiparity, multiple births, advanced maternal age, premature delivery, low education, cesarean section, and stillbirth are potential factors associated with PPH [15-17]. For obstetricians, the accurate identification of indicators affecting PPH in pregnant women and assessment of PPH risk aid in making timely intervention and preventing the occurrence of PPH. This study was conducted at Lhasa People's Hospital from December 2010 to December 2016. The aim of this study was to clarify the incidence of PPH and the factors leading to it in pregnant women in Tibet. Our study findings could provide a reference for clinicians to prevent PPH in pregnant women in this region.

# **Material and Methods**

## **Study Design and Patients**

This was a retrospective study conducted at the Department of Obstetrics and Gynecology in Lhasa People's Hospital from December 2010 to December 2016. A total of 6780 pregnant women who were registered in hospitals or health centers in Tibet were selected for the study. Among them, patients who met the inclusion criteria of gestational age of 28 weeks or more were included. Patients with missing data regarding the volume of PPH, delivery mode, maternal age, prenatal complications, neonatal weight, neonatal head circumference, placental weight, number of fetus, and laboratory inspection indexes were excluded. Ultimately, 4796 women were involved in this study. PPH was diagnosed based on the WHO diagnostic criteria: blood loss >500 mL within 24 h after vaginal delivery or blood loss >1000 mL within 24 h after cesarean section [18]. Participants were divided into a PPH group (n=95) and non-PPH group (n=4701) based on whether PPH occurred. Informed consent was collected from the patients, and the study was approved by the Ethics Committee of Lhasa People's Hospital (approval No. SYLL2218005).

### **Data Collection**

Sociodemographic and clinical data were collected from all patients. Sociodemographic information included the patients' age, place of residence, level of education, number of fullterm births, history of preterm births, and history of abortion. Clinical data included prenatal laboratory indexes, prenatal complications, gestational age, number of fetuses, number of prenatal examinations, placental weight, prenatal length of hospital stay, mode of delivery, perineal condition, neonatal weight and head circumference, neonatal asphyxia, and amniotic fluid condition.

#### Sampling Techniques and Tools

The volumetric, gravimetric, and suction canister methods, 3 commonly used methods of measuring blood loss volume, were used in our study. The volumetric and gravimetric methods are suitable for vaginal delivery while the suction canister method is suitable for cesarean section.

The volumetric method was conducted as follows: after delivery, when the amniotic fluid was drained away, a special kidney basin was immediately placed close to the perineum of the puerpera. After 2 h, the blood container was taken out and the blood volume was measured using a measuring cup.

The gravimetric method was conducted as follows: after delivery, the blood-soaked dressing, sheets, and towels used were collected, sealed, and weighed. The weight of dressing before delivery was subtracted from the weight after delivery. The blood volume was calculated in line with a ratio of weight (g): volume (mL) of 1.05: 1.

After conversion into milliliters, the volume of blood for vaginal delivery was obtained by adding the volume of bleeding from the volumetric and gravimetric methods. The suction canister method was conducted as follows: first, after cutting the uterine wall of the puerpera, the amniotic fluid was sucked out. Next, the blood was collected using suction canisters, poured into a measuring cylinder, and the volume of blood was measured.

## **Statistical Analysis**

For baseline data analysis, the normality of measurement data was evaluated using the Shapiro test. The measurements of normally distributed data were expressed as mean±standard deviation, and comparisons between groups were conducted using the *t* test. Non-normally distributed data were exhibited as median and interguartile range, and the Mann-Whitney U test was employed for comparison between groups. The enumeration data were described as cases and frequency (n [%]), and comparisons between groups were conducted by the chisquared or Fisher's exact test. The related risk factors of PPH were analyzed by logistic regression. A backward stepwise elimination procedure was applied to remove variables with a criterion of P>0.05. MedCalc version 18.11.3 (MedCalc Software bvba, Ostend, Belgium) was used for conducting the receiver operating characteristic (ROC) curves. The optimum cut-off value was selected according to the quantity corresponding to the maximum value of the Youden's index (Youden's index =sensitivity+specificity-1). All statistical analyses were executed using SPSS version 20.0 software. P values of <0.05 were considered to indicate statistical significance.

# Results

## **Overall Basic Patient Information**

In total, 6780 pregnant women in Tibet were involved in our study. After excluding patients with missing data on the volume of PPH (361), delivery mode (346), neonatal weight (343), neonatal head circumference (29), neonatal asphyxia (8), maternal age (181), place of residence (3), number of prenatal examinations (1), placental weight (239), prenatal complications (166), number of fetuses (197), and laboratory indexes (110), 4796 women participated in our study. The patient screening process is shown in **Figure 1**.

As presented in **Table 1**, among the 4796 patients, 90.43% were 18 to 35 years old and 9.57% were  $\geq$ 35 years old. A total of 2265 patients (47.23%) came from urban areas and 2531 (52.77%) came from rural areas. A total of 2340 (48.79%) had a high school education or above and 2456 (51.21%) had junior high school education or below. Some patients (13.78%) had a history of preterm birth, 24.69% of patients had a history of abortion, and most patients had experienced from 1 to 3 full-term births (55.09%). PPH occurred in 95 women, with an incidence of 1.98%.



Figure 1. Flow chart of the detailed selection of patients in the study.

### **Univariate Analysis for PPH**

We performed a univariate analysis for comparing the demographic and clinical characteristics of participants in the PPH and non-PPH groups. The results showed that the percentage of women with the following characteristics was markedly higher in the PPH group than in the non-PPH group:  $\geq$ 35 years old ( $\chi^2$ =21.16, *P*<0.001), full-term birth (*P*=0.003), history of preterm birth ( $\chi^2$ =20.11, *P*=0.001), history of abortion ( $\chi^2$ =11.58, *P*=0.022), condition of the perineum ( $\chi^2$ =56.72, *P*<0.001), cesarean section ( $\chi^2$ =89.80, *P*<0.001), neonatal weight >4 kg (*P*<0.001), placenta weight  $\geq$ 600 g ( $\chi^2$ =6.13, *P*=0.013), neonatal asphysia (*P*=0.003), other inflammation ( $\chi^2$ =5.82, *P*=0.016), amniotic fluid meconium contamination ( $\chi^2$ =6.71, *P*<0.001), and prenatal length of hospital stay (*t*=-4.16, *P*<0.001) (**Table 1**).

## **Multivariable Logistic Regression Analysis for PPH**

Variables with statistically significant differences, according to the results of the univariate analysis, were included in the multivariable logistic regression analysis. As shown in **Table 2**, maternal age  $\geq$ 35 years (odds ratio [OR]=1.96; 95% confidence interval [CI], 1.18-3.27; *P*=0.010); history of preterm birth (OR=2.66; 95% CI, 1.60-4.42; *P*<0.001); cesarean section (OR=6.69; 95% CI, 4.30-10.40; *P*<0.001), neonatal weight >4 kg (OR=3.92; 95% CI, 1.75-8.81; *P*<0.001), and occurrence of neonatal asphyxia (OR=5.52; 95% CI, 2.22-13.74; *P*<0.001) may elevate the risk of PPH in pregnant women.

#### **Construction and Validation of the PPH Prediction Model**

Independent risk factors including maternal age  $\geq$ 35 years, history of preterm birth, cesarean section, neonatal weight

Table 1. Univariate analysis of influencing indicators of postpartum hemorrhage (PPH) in Tibet.

Variables		PPH group (n=4701)		PH group =95)	Statistical magnitude	Р	
Maternal age, n (%)					χ <sup>2</sup> =21.155	<0.001	
<35	4264	(90.70)	73	(76.84)			
≥35	437	(9.30)	22	(23.16)			
Place of residence, n (%)					χ²=0.873	0.454	
Rural area	2490	(52.97)	41	(43.16)			
Urban area	2211	(47.03)	54	(56.84)			
Education, n (%)					χ²=9.755	0.053	
Junior high school or below	2398	(51.01)	58	(61.05)			
High school or above	2303	(48.99)	37	(38.95)			
History of pregnancy							
Full-term birth, n (%)					-	0.003	
0	1955	(41.59)	28	(29.47)			
1-3	2584	(54.97)	58	(61.05)			
≥4	162	(3.45)	9	(9.47)			
Preterm birth, n (%)					χ <sup>2</sup> =20.105	0.001	
No	4064	(86.45)	71	(74.74)			
Yes	637	(13.55)	24	(25.26)			
Abortion, n (%)					χ <sup>2</sup> =11.575	0.022	
No	3550	(75.52)	62	(65.26)			
Yes	1151	(24.48)	33	(34.74)			
Gestational age, n (%)					_	0.568	
<37	72	(1.53)	2	(2.11)			
37-40	2120	(45.10)	46	(48.42)			
>40	2509	(53.37)	47	(49.47)			
Condition of perineum, n (%)					χ²=56.724	<0.001	
Full	1169	(24.87)	11	(11.58)			
Incision	2280	(48.50)	29	(30.53)			
Laceration	355	(7.55)	8	(8.42)			
Unclear	897	(19.08)	47	(49.47)			
Delivery mode, n (%)					χ²=89.790	<0.001	
Vaginal birth	4123	(87.70)	52	(54.74)			
Cesarean section	578	(12.30)	43	(45.26)			
Number of fetuses, n (%)					_	0.059	
Single birth	4683	(99.62)	93	(97.89)			
Multiple births	18	(0.38)	2	(2.11)			

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## Table 1 continued. Univariate analysis of influencing indicators of postpartum hemorrhage (PPH) in Tibet.

Variables	PPH (n=	group 4701)	Non-Pl (n	PH group =95)	Statistical magnitude	Р
Neonatal weight, n (%)					-	<0.001
≤4	4628	(98.45)	87	(91.58)		
>4	73	(1.55)	8	(8.42)		
Neonatal head circumference, n (%)					χ²=0.770	0.380
<34.0	1892	(40.25)	34	(35.79)		
≥34.0	2809	(59.75)	61	(64.21)		
Placental weight, n (%)					χ²=6.130	0.013
<600	2335	(49.67)	35	(36.84)		
≥600	2366	(50.33)	60	(63.16)		
Neonatal asphyxia, n (%)					-	0.003
No	4632	(98.53)	89	(93.68)		
Yes	69	(1.47)	6	(6.32)		
Number of prenatal examinations, n (%)					χ²=1.192	0.275
<5	1390	(29.57)	33	(34.74)		
≥5	3311	(70.43)	62	(65.26)		
Prenatal complications					-	
ICP, n (%)						0.448
No	4605	(97.96)	92	(96.84)		
Yes	96	(2.04)	3	(3.16)		
Anemia, n (%)					χ <sup>2</sup> =0.519	0.471
No	3981	(84.68)	83	(87.37)		
Yes	720	(15.32)	12	(12.63)		
Hypertension, n (%)					-	0.299
No	4586	(97.55)	91	(95.79)		
Yes	115	(2.45)	4	(4.21)		
Eclampsia, n (%)					χ <sup>2</sup> =0.608	0.436
No	4298	(91.43)	89	(93.68)		
Yes	403	(8.57)	6	(6.32)		
Thrombocytopenia, n (%)					-	1.000
No	4674	(99.43)	95	(100.0)		
Yes	27	(0.57)	0	(0.00)		
HBV, n (%)					_	0.117
No	4508	(95.89)	88	(92.63)		
Yes	193	(4.11)	7	(7.37)		

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Table 1	continued.	Univariate and	lvsis of	<sup>f</sup> influencing	indicators of	postpartum	hemorrhage	(PPH) ir	n Tibet.
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Variables	PPH group (n=4701)	Non-PPH group (n=95)	Statistical magnitude	Р
Other inflammation, n (%)			χ²=5.816	0.016
No	4143 (88.13)	117 (84.78)		
Yes	558 (11.87)	21 (15.22)		
Laboratory inspection indexes				
Hb, (mean±SD)	122.59±17.09	122.11±19.03	t=0.28	0.783
RBC, (mean±SD)	3.80±0.58	3.74±0.59	t=1.01	0.315
HCT, (mean±SD)	38.53±9.21	37.71±5.30	t=1.47	0.144
PLT, (mean±SD)	185.76±60.05	175.34±66.65	t=1.67	0.095
Bacterial vaginosis, n (%)			χ²=0.77	0.381
Negative	422 (8.98)	11 (11.58)		
Positive	4279 (91.02)	84 (88.42)		
Amniotic fluid condition, n (%)			χ²=6.713	0.010
Clear	4345 (92.43)	81 (85.26)		
Polluted	356 (7.57)	14 (14.74)		
Prenatal LOS, (mean±SD)	7.38±4.48	9.32±4.76	t=-4.16	<0.001

PPH – postpartum hemorrhage; ICP – intrahepatic cholestasis during pregnancy; HBV – hepatitis B virus; Hb – hemoglobin; RBC – red blood cell; HCT – hematocrit; PLT – platelets; LOS – length of stay.

Table 2. Logistic regression analysis of influencing factors of postpartum hemorrhage (PPH) in Tibet.

Variables	Р	Crude OR (95% CI)	Р	Adjective OR (95% CI)
Maternal age (≥35)	<0.001	2.600 (1.704-3.956)	0.010	1.963 (1.178-3.269)
History of preterm birth (yes)	0.001	2.360 (1.605-3.475)	<0.001	2.656 (1.596-4.420)
Delivery mode (Cesarean section)	<0.001	5.899 (3.902-8.917)	<0.001	6.682 (4.295-10.395)
Neonatal weight (>4 kg)	<0.001	10.470 (6.118-17.931)	<0.001	3.922 (1.746-8.811)
Neonatal asphyxia (yes)	0.003	4.510 (2.123-9.597)	<0.001	5.517 (2.216-13.736)

PPH - postpartum hemorrhage; SE - standard error; OR - odds ratio; CI - confidence interval.

>4 kg, and occurrence of neonatal asphyxia were used to establish the prediction model of PPH. As displayed in Table 2, the PPH prediction model was obtained as follows: Y=Logit (*P*)=-3.184+0.674×maternal age ( $\geq$ 35)+0.977×history of preterm birth (yes)+0.950×mode of delivery (cesarean section)+0.683×neonatal weight (>4 kg)+1.708×neonatal asphyxia (yes). When *P*>0.021, the model predicted that PPH would occur. The results from the ROC curve indicated that the area under the curve (AUC) value of this model was 0.720 (95% Cl, 0.707-0.732; sensitivity, 57.89%; specificity, 83.02%) (**Figure 2, Table 3**).

## Discussion

The sociodemographic and clinical data of 4796 pregnant women in Tibet were collected to measure the incidence of PPH and assess its risk factors in this region. The results showed that the incidence of PPH in Tibet was 1.98%, which was lower than that in some other developing countries, such as Pakistan (6%) [14], Uganda (7.4%) [19], and India (22.7%) [20], and some developed countries, such as Japan (8.7%) [10]. The incidence of PPH varies in different countries and regions owing to differences in economic and social development levels, living habits, ethnicity, and medical and health conditions. There Table 3. The results of receiver operating characteristic (ROC) analysis of the prediction model of postpartum hemorrhage (PPH).

	AUC (95% CI)	SE	Sensitivity (95% CI)	Specificity (95% CI)	Cut-Off
Prediction	0.720 (0.707-0.732)	0.029	57.89 (47.3-68.0)	83.02 (81.9-84.1)	0.021

AUC – area under curve; ROC – receiver operating characteristics; PPH – postpartum hemorrhage; CI – confidence interval; SE – standard error.



**Figure 2.** Receiver operating characteristic (ROC) curve showing the efficacy of the postpartum hemorrhage (PPH) prediction model.

were confounding and selection biases in the study samples because only patients registered in hospitals or health centers in Tibet were included to analyze the incidence of PPH, which might have caused the difference in incidence between Tibet and other areas. In this study, maternal age  $\geq$ 35 years, history of preterm birth, cesarean section, neonatal weight >4 kg, and occurrence of neonatal asphyxia were identified as risk factors for PPH in pregnant women in Tibet.

In the present work, maternal age  $\geq$ 35 was identified to increase the risk of PPH by 0.96 times. Advanced maternal age leads to a higher risk of PPH [21-23], which can be caused by the decrease in elasticity of the soft birth canal and worsening of uterine contraction with the increase of maternal age. Also, a higher risk of placenta previa and placental abruption occur with advanced maternal age, which increase the possibility of PPH [24]. In our present study, preterm birth was also a risk factor for PPH, and this was supported by the results of several previous studies [25-28]. The present results showed that women with a history of preterm birth exhibited 1.66 times higher risk of having PPH than those without a history of preterm birth. The reason may be that women with preterm deliveries often have pregnancy complications such as placenta

previa and premature rupture of membranes, which cause endometrial damage and increase the risk of bleeding [29,30].

Cesarean section is a common choice for obstetricians when they face emergencies such as dystocia. However, the risk of a severe complication such as bleeding, thromboembolism, and infection is much higher in women delivering by cesarean section than by vaginal birth [31]. Previous studies have revealed that compared with vaginal delivery, cesarean section has a significantly higher risk of PPH [14,32], which supports the conclusion of our study. Cesarean section, as an invasive operation, can cause mechanical injury to the body and can cause irritable coagulation disorders. The timing of the cesarean section operation is an important factor affecting the volume of bleeding. Seligman et al indicated that women receiving cesarean sections during delivery often had a higher risk of PPH, compared with women having prenatal cesarean sections [33]. This may be because cesarean sections are often the choice after vaginal delivery failure due to various reasons, such as fetal asphyxia. A long stage of labor results in edema of uterine myofiber, brittleness and thinning of the lower segment of the uterus, and poor uterine contraction, which increase blood loss. In addition, cesarean section can prolong the operation time of parturient women, increasing the volume of blood loss.

In the present study, the data showed that neonatal weight >4 kg could increase the risk of PPH in pregnant women by 2.92 times and was an independent risk factor for PPH. Neonatal weight >4 kg, namely macrosomia, was identified as being associated with the risk of PPH in previous studies. A retrospective cohort study by Davey et al including all pregnant women in Victoria, Australia, demonstrated that macrosomia increases the risk of severe PPH in pregnant women [34]. Another prospective cohort study showed that macrosomia increases the risk of PPH in women in Uganda by 1.18 times [14]. A casecontrolled study indicated that fetal macrosomia resulted in more frequent PPH in pregnant women in Tanzania [35]. With the development of the social economy, the living standards of people are generally improved, and pregnant women pay more attention to nutrition and supplementation during pregnancy. Improper nutrition and lack of enough physical exercise make not only pregnant women themselves gain excessive weight, but also increase the risk of macrosomia in the fetus. An oversized fetus is likely to lead to excessive distension of uterine fibers, thinning of the myometrial wall, and poor myofiber contraction, resulting in PPH [14,36]. During vaginal delivery, macrosomia may prolong the first and second stages of labor and result in severe perineal laceration or even perineal incision. When the laboring trial period is too long, obstetricians often choose cesarean section to avoid neonatal asphyxia. Another risk factor for PPH in pregnant women is neonatal asphyxia, which is one of the most serious situations encountered in the clinic [37]. Neonatal asphyxia is associated with advanced maternal age, malpresentation, and prolonged labor process, which all increase the rate of cesarean section and the risk of PPH [38,39]. Closely monitoring fetal heart changes and observing the amniotic fluid for meconium contamination can identify early fetal distress to prevent PPH in time.

A PPH prediction model was successfully established as follows: Y=Logit (*P*)=-3.184+0.674×maternal age ( $\geq$ 35)+0.977×history of preterm birth (yes)+0.950×mode of delivery (cesarean section)+0.683×neonatal weight (>4 kg)+1.708×neonatal asphyxia (yes). The best cut-off value was 0.021. When the value of *P*>0.021, the model predicted PPH would occur. For the validation of the PPH prediction model, the AUC value, sensitivity, and specificity indicated that the model could determine whether PPH will occur in patients. Therefore, it has potential value for the use in the clinic setting.

Our study has some limitations. This study included women who received care in different levels of medical institutions, including Grade A urban tertiary hospitals, ordinary county hospitals, and township health centers. The different conditions

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of the hospitals resulted in a difference in measured postpartum blood loss of the women included in this study. This might have been affected by the regional economies and whether a health care system was well established, among other factors.

## Conclusions

Despite significant improvements in biomedicine and reproductive health services and measures such as oxytocin used by obstetricians, PPH rates remain high. In our study, we found maternal age  $\geq$ 35 years, history of preterm birth, cesarean section, newborn weight >4 kg, and occurrence of neonatal asphyxia were risk factors for PPH in pregnant women in Tibet. These results should remind obstetricians to be especially alert to these risk factors in the prenatal and perinatal period and to provide timely intervention for pregnant women with a high risk of PPH. Obstetricians should make detailed assessments of pregnant women to prevent PPH and optimize pregnancy outcomes.

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### **Conflict of Interests**

None.

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