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Original Research

Predicting adverse outcomes of hypertensive disorders in pregnancy: validation of fullPIERS model in Chinese population

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Summary

Purpose of Investigation: The fullPIERS model is an effective tool to predict the adverse outcomes of pre-eclampsia. This study aimed to validate the effectiveness of fullPIERS model, and discover the variables that may be useful to predict the adverse outcomes of hypertensive disorders in pregnancy (HDPs) in Chinese population. *Materials and Methods:* The authors retrospectively collected the data of 1,430 HDPs patients within 48 hours of adverse outcomes in two tertiary hospitals in China. Calculated the risk probability value of every patient using fullPIERS model and validated the predictive efficiency by area under curve of operating characteristic curve (AUC ROC). To assess the factors particularly useful to predict adverse outcomes of HDPs for Chinese population, the authors conducted the independent sample *t*-test and multivariate regression analysis to the following factors: age, platelet count, gestational age, creatinine, AST, total bilirubin, direct bilirubin, indirect bilirubin, hemoglobin, albumin, globulin, ALT, alkaline phosphatase, lactic dehydrogenase, urea, and uric acid. *Results:* The AUC ROC was 0.768 calculated by fullPIERS model within 48 hours of adverse outcomes, and the cut-off probability value was 0.045. In patients with a probability value ≥ 0.045, 53.53% experienced adverse outcomes, and the false positive rate was 10.70%. Lactic dehydrogenase was a promising variable for predicting the risk of adverse outcome of HDPs. The AUC ROC calculated based on lactic dehydrogenase alone was 0.615 with a cut-off value of 243.5 U/L. *Conclusions:* The fullPIERS model was effective for Chinese population to predict adverse outcomes in pregnant women complicating HDPs. Lactic dehydrogenase was a promising variable to predict the adverse outcomes of HDPs.

Key words: Hypertensive disorders in pregnancy; FullPIERS model; Adverse outcome; Risk prediction.

Introduction

Hypertensive disorders in pregnancy (HDPs), including preeclampsia, eclampsia, gestational hypertension, chronic hypertension, and HELLP syndrome, complicating 5-10% of pregnancies [1], are important causes of mortality and morbidity in pregnant women. The pathogenesis of HDPs is unclear. Therefore, no effective treatment can be used except delivery. However, for those patients suffering remotely from term, the magnitude of the maternal risks associated with expectant management is unclear [2].

Professor Peter von Dadelszen *et al.* at the University of British Columbia in Vancouver, Canada, developed the fullPIERS model, based on maternal demographics, signs, symptoms, and laboratory tests, to predict the risk of adverse outcome of pre-eclampsia under the collaboration of eight international centers in six years [3]. Both the internal and external validation of fullPIERS model have been proven by some studies [3-6]. Therefore, the study's aim was to validate the effectiveness of fullPIERS model for the Chinese population, and to discover the variables which may be useful to predict the risk of adverse outcome of HDPs in this population.

Materials and Methods

Women diagnosed as HDPs and admitted to the First Affiliated Hospital of Soochow University (hospital 1) between January 2007 and May 2011 (606 cases), the Suzhou Municipal Hospital (hospital 2) between January 2007 and October 2012 (824 cases) were chosen for the study. Both the two are tertiary hospitals located in Jiangsu province, China. The definition of HDPs is based on the guideline built by International Society for the Study of Hypertension in Pregnancy (ISSHP) [7].

The adverse outcomes of patients referred to Delphi consensus for the fullPIERS model developed [8, 9], including maternal mortality, or one of the following morbidities: hepatic dysfunction, hematoma, or rupture, one or more seizures of eclampsia, Glasgow coma score < 13, stroke, reversible ischemic neurological deficit, transient ischemic attack, posterior reversible encephalopathy syndrome, cortical blindness or retinal detachment, need positive inotrope support, infusion of a third parenteral antihypertensive, myocardial ischemia or infarction, acute renal insufficiency or failure, dialysis, pulmonary edema, SpO_2 < 90%, requirement of ≥ 50% fractional inspired oxygen (FiO_2) for more than one hour, intubation (other than solely for caesarean section), transfusion of any blood product, severe thrombocytopenia (< 50*109/l) in the absence of blood transfusion, and placental abruption. The fullPIERS logistic regression equation for the prediction of adverse maternal outcomes is [3]: logit (pi) = 2.68 + (-5.41×10^{-2} × gestational age at eligibility)+1.23 (chest pain or

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dyspnea) + (−2.71 × 10^{-2} × creatinine) + (2.07×10^{-1} × platelets) + (4.00×10^{-5} × platelets^2) + (1.01×10^{-2} × AST) + (−3.05 × 10^{-6}, AST^2) + (2.50×10^{-4} × creatinine × platelets) + (−6.99× 10^{-5} × platelets × AST)+(−2.56 × 10^{-3} × platelets × SpO_2). We also found the values of SpO_2 were especially omitted. To be consistent with the fullPIERS study, missing SpO_2 values were imputed to 97%, the population median for women without adverse outcomes. All the definitions of adverse outcomes and the fullPIERS probability calculator are available on the study website: https://piers.cfri.ca. The authors retrospectively collected the medical records data of the enrolled patients within 48 hours of adverse outcomes, including maternal symptoms, laboratory tests and pregnancy outcomes.

For all patients included, the authors calculated the probability value with fullPIERS model and analyzed the applicability to predict adverse outcomes of HDPs by the area under the curve of the receiver operating characteristics curve (AUC ROC). AUC ROC was interpreted using five categories [10]: non-informative (AUC = 0.5), poor accuracy (0.5 < AUC< 0.7), moderate accuracy (0.7 < AUC <0.9), high accuracy (0.9 < AUC < 1), and perfect accuracy (AUC = 1).

In addition, to screen the factors particular useful for the present population to predict adverse outcomes of HDPs, the authors conducted the independent sample *t*-test and multivariate regression analysis to the following factors: age, platelet count, gestational age, creatinine, aspartate transaminase (AST), total bilirubin, direct bilirubin, indirect bilirubin, hemoglobin, albumin, globulin, alanine transaminase (ALT), alkaline phosphatase, lactic dehydrogenase, and urea and uric acid. All the analyses were conducted by SPSS22.0. *P* value < 0.05 was considered significant.

Results

The study enrolled 1,430 patients in total, including 51 cases of eclampsia, 1,221 cases of severe pre-eclampsia, 124 cases of mild pre-eclampsia, and 34 cases of pregnant hypertension (Table 1). Of all the patients, 262 (18.32%) patients experienced adverse outcomes, and of which one patient that died, 37 patients complicated with two kinds of adverse outcomes, and 14 cases complicated with three or more kinds of adverse outcomes (Table 2).

With the variables obtained 48 hours prior to the appearance of adverse outcomes, the calculated AUC ROC was 0.768 ($p < 0.05$), with the probability cut-off value of 0.045. The probability values and corresponding pregnancy outcomes are shown in Table 3.

Nine hundred thirty-one (65.10%, 931/1,430) patients had a probability value < 0.025, of which 80 patients (8.59%, 80/961) complicated with adverse outcomes. When the probability value ≥ 0.15, ≥ 0.20, and ≥ 0.30, the percent of patients were 5.56%, 4.06%, 2.38% respectively, and the corresponding incidence of adverse outcomes were 82.72%, 89.66%, and 94.12%. Considering the result of AUC ROC, there were 269 (18.81%, 269/1,430) patients who had the probability value ≥ 0.045, of which 144 (53.53%) patients experienced adverse outcomes, and the false positive rate (FPR) was 10.7%. Therefore, obstetrician should attach importance to those with a probability value ≥ 0.045.

Table 1. — *The distribution of 1,430 patients with hypertensive disorders in pregnancy.*

Hospitals	Total number	Eclampsia	Severe pre-eclampsia	Mild pre-eclampsia	Gestational hypertension
1†	606	45	413	119	29
2‡	824	6	808	5	5
Total number	1430	51	1221	124	34

1† refers the first affiliated hospital of Soochow University. 2‡ refers to the Suzhou Municipal Hospital.

Table 2. — *The distribution of adverse outcomes.*

Adverse outcomes	Hospital 1	Hospital 2
Maternal death	1	0
Induced labor/abortion	30	7
Stillbirth/dead fetuses	29	14
Eclampsia	45	6
Stroke/ reversible ischemic neurological deficit	4	0
Cortical blindness/retinal detachment	5	10
HELLP syndrome	18	23
Heart failure	26	6
Need for positive inotrope support	4	0
Infusion of a third parenteral antihypertensive	15	0
SpO_2 < 90%	11	2
Requirement of ≥ 50% fractional inspired oxygen	3	0
Disseminated intravascular coagulation (DIC)	0	1
Intubation (other than solely for cesarean section)	5	0
Pulmonary edema	1	3
Transfusion of any blood product	1	6
Severe thrombocytopenia (< 50*109/l) without blood transfusion	18	2
Acute renal insufficiency or failure	14	19
Hepatic dysfunction	0	13
Dialysis	6	0
Placental abruption	30	13
2 kinds of adverse outcomes above	20	17
≥ 3 kinds of adverse outcomes above	11	3

To validate the fullPIERS at different time window, the authors divided all the 1,430 patients into three groups according to the time interval between the moment of attaining predictive variables and the appearance of adverse outcomes: six hours (278 patients), 24 hours (437 patients), and 48 hours (715 patients), and calculated the AUC ROC in the three time-points, respectively. The results were as follows: (1) six hours: the AUC ROC with a cut-off probability value of 0.061, of the 48 cases (17.27%) with probability value ≥ 0.061, 34 cases (70.83%) complicated adverse outcomes, the FPR was 5.6%; (2) 24 hours: the AUC ROC with a cut-off value of 0.054, of the 101 cases (23.11%) with probability ≥ 0.054, 60 cases (59.41%) complicated the adverse outcomes, and the FPR was 12%; (3)

Table 3. — *Distribution of women with and without adverse outcomes according to predicated probability value calculated by fullPIERS model within 48 hours of adverse outcomes.*

Probability range	Number of women in range [n. (%)]	Women with adverse outcome(s) [n. (%)]	Women without adverse outcome(s) [n. (%)]	True positive rate (%)	False positive rate (%)
0-0.0049	154 (10.77)	14 (9.09)	140 (90.91)	-	-
0.005-0.0099	326 (22.80)	26 (7.98)	300 (92.02)	94.66	88.01
0.01-0.0149	219 (15.31)	20 (9.13)	199 (90.87)	84.73	62.33
0.015-0.0199	143 (10.00)	11 (7.69)	132 (92.31)	77.1	45.29
0.02-0.0249	89 (6.22)	9 (10.11)	80 (89.89)	72.9	33.99
0-0.0249	931 (65.10)	80 (8.59)	851 (91.41)	-	-
0.025-0.0299	96 (6.71)	16 (16.67)	80 (83.33)	69.47	27.14
0.03-0.0349	55 (3.85)	10 (18.18)	45 (81.82)	63.36	20.29
0.035-0.0399	47 (3.29)	11 (23.40)	36 (76.60)	59.54	16.44
0.04-0.0449	32 (2.23)	1 (3.13)	31 (96.87)	55.34	13.36
0.045-0.0499	36 (2.52)	8 (22.22)	28 (77.78)	54.96	10.7
0.05-0.099	116 (8.11)	45 (38.79)	71 (61.21)	56.2	8.3
0.1-0.0149	36 (2.52)	24 (66.67)	12 (33.33)	34.73	2.23
> 0.15	81 (5.66)	67 (82.72)	14 (17.28)	25.57	1.2
> 0.20	58 (4.06)	52 (89.66)	6 (10.34)	19.85	0.51
> 0.30	34 (2.38)	32 (94.12)	2 (5.88)	12.21	0.17
Total (n.)	1430	262	1168		

Table 4. — *Laboratory results and probability value calculated by fullPIERS model of the nine extreme cases.*

Category	case	Gestational age (week)	The laboratory results of within 48 hours of women with adverse outcome(s)				Probability value
			SpO_2 (%)	Platelet account (*10^9/L)	Creatinine (μmol/ L)	AST (U/L)	
Cases of small probability value with the adverse outcome(s)	Death	38^{+0}	80	47	360	160	0.086
	Eclampsia	38^{+0}	97	283	46	26	0.002
	Pulmonary edema combined	34^{+2}	97	313	66	194	0.002
	Placenta abruption with HELLP syndrome	33^{+0}	97	422	44	49	0.001
	Placenta abruption	36^{+0}	97	246	32	31	0.002
	Placenta abruption	37^{+0}	97	239	29	13	0.002
	Placenta abruption	31^{+6}	97	364	45	16	0.002
	Placenta abruption	39^{+4}	97	376	31	15	0.002
Case of large probability value without adverse outcome		33^{+4}	93	419	86	42	0.867

48 hours: the AUC ROC with a cut-off probability value of 0.041, of the 113 cases (15.80%) with probability value ≥ 0.041, 45 cases (39.82%) complicated adverse outcomes, the FPR was 11%.

Special adverse outcomes such as using three or more kinds of antihypertensive and blood transfusion were also included in the adverse outcomes. However, there was no standardization in managing the two circumstances in clinic. To decrease the error caused by the two situations, the authors respectively calculated the AUC ROC without the cases of using three or more antihypertensive drugs and blood transfusion. The former was 0.768, showing no difference with the AUC ROC calculated by all the cases ($p > 0.05$), while the latter was 0.769, larger than the AUC ROC calculated by the whole cases ($p < 0.05$). In addition, the present study included nine extreme cases listed in Table 4. When the values of platelet account, creatinine, AST were adjusted into the normal range in the death case (the first case in Table 4), and the case complicated neither adverse outcome (the last case in Table 4), the recalculated probability values of the two cases were 0.99 and 0.294, respectively. At the same time, the authors found that in the nine extreme cases, the values of gestational age, platelet account, creatinine, and AST were almost in the normal range, yet the values of albumin, alkaline phosphatase, lactic dehydrogenase, and uric acid all showed different degree of abnormality. When removing the nine extreme cases, the AUC ROC was 0.792, larger than 0.768 ($p < 0.05$), which improved the prediction effectiveness of fullPIERS model. Removing both the one case of blood transfusion and the nine extreme cases, the AUC of ROC was 0.793, larger than 0.768 as well ($p < 0.05$).

The authors found that when the AUC ROC was calculated by the all cases (1,430), 53.53% of the cases with the probability value ≥ 0.045 experienced adverse outcomes, while the AUC ROC calculated by the cases of variable ob-

tained within six hours of adverse outcomes (278), 70.83% of the cases experienced the adverse outcomes. Analyzing the variables between the two groups, the authors found that the cases of probability value < 0.045, but accompanied with adverse outcomes showed almost normal values of gestational age, platelet account, AST, and creatinine; the cases of probability value ≥ 0.061 and without adverse outcomes showed an decreased platelet account and low value of AST, and the value of creatinine was in normal range. Nonetheless, majority of the cases above showed almost normal values of the following items: albumin, alkaline phosphatase, lactic dehydrogenase, and uric acid, which illustrated perhaps some potential relation existing in factors of gestational age, platelet account, AST and creatinine, or some unknown factors either influencing the prediction effect. Furthermore, the authors made the comparison between the two groups using independent sample *t*-test, and found that gestational age, platelet account, TBIL, DBIL, IBIL, alkaline phosphatase, lactic dehydrogenase, creatinine, and uric acid showed differences ($p < 0.05$), while age of patients, hemoglobin, total protein, globulin, and urea showed no difference ($p > 0.05$). Then the authors made a multivariate logistic regression analysis using the significant variables above, and found that gestation age, creatinine, platelet account, AST, and lactic dehydrogenase indicated a statistical significance ($p < 0.05$). Therefore, the authors thought except for the variables in the fullPIERS model, lactic dehydrogenase might be used to predict the adverse outcomes of HDPs for this population as well. They calculated the AUC ROC using lactic dehydrogenase alone and the result was 0.615 ($p > 0.05$) and the cut-off value of lactic dehydrogenase was 243.5 U/L.

Discussion

HDPs is the second reason for the death of pregnant women in the world [11] and the third in China [12]. At present, for those patients remote from term, expectant management may bring benefits such as the optimum antenatal corticosteroid effect, and offers the opportunity for those severe patients of being transferred to a higher-level facility. Therefore it is necessary to predict the prognostic risk of HDPs with a high-effective tool, so as to optimize the management plan and the time of terminating.

Previous model was unsuccessful to predict of adverse outcomes occurring at any time after admission with preeclampsia [13]. Some common indexes such as mean arterial pressure (MAP), roll over test (ROT), 24-hour ambulatory blood pressure monitoring, the monitoring system for hypertension, and Doppler ultrasonic monitor used clinically to predict the progress of HDPs all showed unsatisfactory effect [14].

In 2011, Professor Peter von Dadelszen *et al.* [3] developed the fullPIERS model based on the Caucasian to identify the risk of fetal and life-threatening complications in women with pre-eclampsia within 48 hours of hospital admission. They internally validated the effectiveness of the model to predict adverse outcomes within 48 hours with the AUC ROC of 0.88 (95% CI 0.84–0.92). Akkermans *et al.* [5] externally validated the model using prospectively collected data from two tertiary care obstetric centers, and found the fullPIERS model could predict adverse maternal outcomes within 48 hours (AUC ROC 0.97, 95% CI: 0.87–0.99) and up to seven days after inclusion (AUC ROC 0.80, 95% CI: 0.70–0.87). Both the two studies illustrated the efficiency of fullPIERS model in the high-income countries.

In the present study, the AUC ROC was 0.768 calculated by fullPIERS model within 48 hours, lower than 0.88 in the original study [3], but likewise reflected a moderate accuracy [10]. In the present study, the cases consisted of not only pre-eclampsia, but gestational hypertension was also included, which may be the reason for the lower cut-off value of probability (0.045) than the original study (0.3) [3]. In patient of probability value ≥ 0.045, 53.53% experienced adverse outcomes with a FPR of 10.70%, which meant doctors should pay close attention to those patients.

Another study validating the efficiency of fullPIERS model based on patients in low- and middle-income countries had similar value of AUC ROC (0.77) to the present (0.768) [6]. It also included the cases of gestational hypertension, which suggested the fullPIERS model was more suitable for the high-income countries, and the low- and middle- income countries should explore the prediction models based on their own patients.

Combination of three or more kinds of antihypertensive and blood transfusion were both considered as adverse outcomes, yet no there is standardized treatment to them clinically in this nation. Therefore the authors removed the cases complicated with the two situations, respectively, and recalculated the AUC ROC, and found that blood transfusion was a factor influencing the prediction effect in this population.

The present authors also found some extreme cases in the study. One patient died and the probability value was 0.086, while another case experienced no adverse outcome with the probability of 0.867, which seemed really strange. Then the authors adjusted the values of platelet account/creatinine/AST into the normal range, the former case's probability value > 0.99, while the latter case's probability turned out to be 0.294. After communicating with Professor Peter von Dadelszen, the present authors discovered that creatinine and platelet levels were not independent factors, presenting some degree of interaction, therefore a slight adjustment was made between the two factors when building the fullPIERS model. In addition, there was no case of death included in their study. Perhaps the fullPIERS model was not fit for such severe cases. The present authors also found one case of eclampsia, one case of pulmonary edema combined with HELLP syndrome, and five cases of placenta abruption; all of them showed a small probability (≤

0.002). Further analysis suggested the values of albumin, lactic dehydrogenase, alkaline phosphatase, and uric acid showed different degree of abnormality in the above cases.

To search for other promising factors influencing prediction efficiency, the authors compared variables between the cases of probability value < 0.045 but accompanied with adverse outcomes and the cases of probability value ≥ 0.061 without adverse outcomes. The results of multivariate logistic regression analysis suggested that gestation age, creatinine, platelet account, AST, and lactic dehydrogenase showed a statistical significance ($p < 0.05$). Therefore, the present authors thought that except for the variables in the fullPIERS model, lactic dehydrogenase could be used to predict the adverse outcomes of HDPs as well. The authors calculated the AUC of ROC using lactic dehydrogenase alone and the result was 0.615 and the cut-off value of lactic dehydrogenase was 243.5 U/L. In addition, the seven cases experienced adverse outcomes while with a small probability value, there were four cases that had lactic dehydrogenase ≥ 243.5U/L, one even up to 1,443U/L, which suggested lactic dehydrogenase may be an effective variable for predicting the adverse outcomes of HDPs.

Conclusion

First this study showed that fullPIERS model was effective in Chinese population to predict adverse outcomes in pregnant women complicated with HDPs. In the patients with probability value ≥ 0.045, 53.53% experienced adverse outcomes within 48 hours, and the FPR was 10.70%, which suggested obstetrician need to pay close attention to those patients. Second, the authors found some severe cases may be not suited for the model, such as cases of death and placenta abruption. Some adjustment of variables need to be made before its use. Third, the authors found lactic dehydrogenase was a promising variable to predict the adverse outcomes of HDPs for this population, which is probably useful in future studies. The present study also had limitations. On the one hand, this study had a relative small sample, which could only validate the effectiveness of the model for this population. If the authors want to build a model which is more suited to this population and more practical in clinics, further samples from nationwide regions are needed. On the other hand, the HDPs in this study consisted of not only severe situation, such as eclampsia and severe pre-eclampsia, but also mild disorders such as mild pre-eclampsia and gestational hypertension. A mixture of disorders may decrease the predictive efficiency of the model. Therefore, future work should study the different disorder of HDPs respectively.

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