DETERMINING THE MATERNAL CHARACTERISTICS THAT PREDICTS THE ADVERSE OUTCOMES FOR PATIENTS WITH PREECLAMPSIA

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ABSTRACT

BACKGROUND:
Preeclampsia is a major cause of maternal morbidity and mortality worldwide. Despite the advances made in the field of obstretics, the ability to predict maternal and neonatal outcome in pregnant women with pre-eclampsia remains under developed.

OBJECTIVE:
To determine the clinical characteristics that could be used as a prognostic tool that would aid in clinical assessments and interventions, which in turn will reduce the rate of mortality in pregnant women with preeclampsia.

METHODS:
This nested case control study enrolled 40 subjects diagnosed clinically with pre-eclampsia. Using logistic regression, we determined the cilinical characteristics that could be used as a prognostic tool.

RESULTS:
Maternal and gestational age were strong predictors that indicate poor prognosis in severe patients with preeclampsia at <37 weeks gestation. The scoring card models developed in this study had good calibration and discrimination value with a $p > 0.05$ and AUC 0.850 (95% CI 0.732 to 0.969). Subjects with total scores of 0, 1, and 2 had 3.1%, 27.6%, and 80.6% poor prognosis, respectively.

CONCLUSION:
Maternal age and gestational age are strong predictors for poor clinical outcomes in patients with preeclampsia.

Keywords**:** *severe preeclampsia, clinical predictor, poor prognosis*

Introduction

Preeclampsia is a pregnancy-specific disorder that occurs in 3 to 5% of all pregnancies (1). This condition remains a major cause of maternal and perinatal, morbidity and mortality and poses a threat to many developing countries worldwide (1). Although several criterias and guidelines for diagnosing and managing pre-eclampsia in pregnant women have been established in recent years, the overall morbidity and mortality have not dramatically changed (2-5). The cause for pre-ecplamsia has been attributed namely due to the cytokines or factors released by the placenta, thus the main strategy for treating this condition is to deliver the placenta from the mother as soon as possible (1). However, in doing so, there are consequential maternal and perinatal risks that need to be weighted. In many instances, while this results in good neonatal outcome, maternal health may still be affected and remains a risk (2,5).

Our ability to predict maternal and perinatal outcomes in pre-eaclampsia to date remains poor, even with advancing technologies that are reported every year (6). In many rural areas, general practitioners (GP) remain the main front-liners that manage pregnant women At times where doctors are not available midwives, with limited diagnostic facilities provide services to pregnant women. It is fortunate

that in many cases, pregnancy is usually uneventful and that most pregnant mothers complete their pregnancies with no complications. The main challenge however, arises when certain condition such as pre-eclampsia occurs. It now becomes necessary for healthcare providers to refer high-risk patients to an appropriate referral centre. In many cases, healthcare providers are pressed into making the correct decision in a short time, and in many instances a wrong call of judgement is inevitable since these are uncommon conditions to manage. This is compounded by the fact that clinical signs alone are not strong indicative and thus is not predictive of the patient outcome and prognosis (6,7). Whilst more sophisticated equipments and devices may be available for use in such instances, many underdeveloped countries and even rural areas may not be able to benefit from it due to the high cost required. Extensive training programs are an option, however, considering that number of healthcare providers are few, and that the cost to ensure exclusive training would be prohibitive for under-developed nations, this option is also unlikely to be possible in the near future. As such, the is an urgent need to develop an easy method for staff of lesser skills to be able to make an early diagnosis, and make predictive outcome and prognosis in order to weigh the consequences of delay referral. Thus the aim of the present study is to establish pre-eclampsia prognostic system based on clinical characteristics for evaluation of the severity and outcome of this condition thereby creating a system by which staff in many underprivellaged healthcare centres may benefit.

Methods

We conducted a prospective nested case control study from September 2011 to August 2012 involving patients at 28-36 weeks of singleton gestation who were diagnosed with severe pre-eclampsia with intrauterine pregnancy carrying a viable fetus. Patients with a history of diabetes mellitus and renal disorder were excluded from this study. Gestational age was determined by history taking (last menstrual period) and biparietal diameter/femur length based on ultrasonography (Mindray DP-1100 Plus). The subjects were said to have pre-eclampsia if blood pressure was ≥160 mm Hg systolic or 110 mm Hg diastolic on two occasions at least 6 h apart during bed rest and proteinuria was 3+ or greater. Obstetric status examination includes uterine fundal height, fetal position, fetal presentation, and estimated birth weight measured (Jhonson Tausak). Written informed consent to participate in the study was obtained from the subjects. The study was approved by the Local Ethical and Research Committees.

All patients (n=40) with pre-eclampsia were admitted, stabilized, evaluated, and planned to have expectant management. Twenty-eight patients (n=28) were found to be unstable in the first 24 hours and required immediate delivery. Corticosteroids were used in all patients before the pregnancies were terminated. Expectant management is defined as conservative management until any complications as the result of PE became apparent, warranting termination of the expectant management (n = 12). Expectant management consisted of bed rest and monitoring of maternal blood pressure every hour and urine output every 4 hour. The patients were questioned frequently about headache, visual disturbance, and right upper quadrant pain. Blood tests included hemoglobin, hemoatocrite, platelet count, serum liver enzymes, ureum, creatinine, uric acid, lactate dehydrogenase and coagulation profile. Oral antihypertensive medication (Nifedipine 30-120 mg per 24 h) was initiated with target <20% decreases in mean arterial pressure. Magnesium sulfate was given as antiseizure. Dexamethasone intramuscular was given for fetal lung maturation. Fetal assessment consisted of initial ultrasonography to estimate gestational age and amniotic fluid index. Fetal heart rate was reassured every 15 minutes. The patients were delivered if contraindication to expectant management developed or when pregnancy has reached 37 weeks. Indication in the foetus to terminate the preganancy ealy (fetal indidcation) was when any signs of fetal distress requiring was observed. The mode of delivery was determined by attending physician based on obstetric and fetal indications.

Data are presented as median or range, as where deemed appropriate. All variables was analyzed using chi square (CI 95%). If $p < 0.05$ in bivariate analysis, we continue to proceed for a multivariate analysis (backward and stepwise) and we choose a prognostic model based on the callibration and discrimination tests. A simulation to count probability and cut off, was performed in order to create a scoring system.

Results

Forty (N=40) subjects who fulfilled our inclusion criteria were recruited for this study. Among them, 28 patients (70%) had immediate delivery and the remaining 12 were managed expectantly. Prolongation time for gestation varied between 24 hours and 171 hours. One patient developed intra-uterine fetal death, i.e patient who underwent 171-hours of prolonged labour. Characteristics of subjects, i.e. maternal age, gestational age, gravida and history of preeclampsia are shown in the table 1.

Table 1. Characteristics of Subjects

Characteristics	**n**	**%**
Maternal age (Year)		
<20 and >35	14	35%
20 – 35	26	65%
Gestational age (weeks)		
28 – 33	23	57.5%
34-36	17	42.5%
Previous Preeclampsia		
(+)	6	15%
(-)	34	85%
Gravida		
Primigravida and Grandemultigravida	14	35%
Multigravida	26	65%

The age group between 20-35 years represented approximately 65% of the subject population. Primigravida and grand-multigravida, i.e. history of more than 4 pregnancies previously, represented 35% of the patients. Previous history of pre-eclampsia was found only in 15% of the recruited subjects.

Eligible variables for multivariate analysis (p<0.25 based on bivariate analysis) were maternal age, gestational age, and previous PE (table 2).

In order to develop a prognostic model using logistic regression (backward stepwise), we included all variables with p < 0.25. Among the four, only two variables were found to be significant (table 3).

Based on Hosmer Lemeshow test, this model was well calibrated with p value of > 0.05 (table 4).

This model was also well discriminated based on the area under the curve (table 5). Discrimination of scoring model was 0.835 (CO 95%; 0.709-0.961).

Table 2. The Result of Bivariate Analysis between All Variable with Prognosis from Severe Preeclampsia < 37 weeks

Variable	Prognosis		n	p Value	OR	CI 95%	
	Poor (<24 hour)	Good (≥ 24 hour)				Min	Max
Maternal age (year)							
20 - 35	9 (22.5%)	17 (42.5%)	26 (65%)	p=0.101	3.4	0.87– 13.239	
<20 & >35	9 (22.5%)	5 (12.5%)	14 (35%)				
Gestational Age							
28 - 33	16 (40%)	7 (17.5%)	23 (54.5%)	P<0.001	17.143	3.06 – 95.9	
34 - 36	2 (5%)	15 (37.5%)	17 (45.5%)				
Previous PE							
No	17 (42.5%)	17 (42.5%)	34 (85%)	p=0.197	0.2	0.21 – 1.897	
Yes	1 (2.5%)	5 (12.5%)	6 (15%)				
Gravida							
Primi& Grande	7 (17.5%)	7 (17.5%)	14 (35%)	p =0.744	1.364	0.370– 5.028	
Multi	11 (27.5%)	15 (37.5%)	26 (65%)				

Table 3. Logistic regression analysis (backward stepwise)

							95% C.I. for EXP(B)	
	B	S.E.	Wald	Df	Sig.	Exp(B)	Lower	Upper
Maternal age	2.092	.932	5.034	1	.025	8.102	1.303	50.386
Gestational age	3.165	1.224	6.692	1	.010	23.700	2.154	260.814
Constant	-3.833	1.257	9.296	1	.002	.022		

Table 3. Subject Probability had Poor Prognosis

Patient Score	Constanta	Coefisien	Y = -3.437 + 2.474 x total score	P= 1 / (1 + exp (-y))
0	-3.437	2.474	-3.437	0.031
1	-3.437	2.474	-0.963	0.276
2	-3.437	2.474	1.511	0.806

Table 4. Hosmer and Lemeshow Test

Step	Chi-square	Df	Sig.
1	2.022	5	.846
2	.428	2	.807

Table 5. Area under the curve

Area	Std. Error	Asymptotic Sig	Asymptotic 95% CI	
			Lower Bound	Upper Bound
.835	.064	.001	.709	.961

We the determined the subject probability of poor prognosis (table 6).

After calculating the probability of poor prognosis, we made a scoring card that could be used in everyday practice.

Based on the area under the curve of the total score desribed above, we were able to create a reference table

(table 7). From table 7, we determined the optimum cut off. At a score greater than 2, the sensitivity was 100% and specificity was 44.4%.

From the table above, we also made a scoring card that could be used daily by our healthcare provider.

Table 6. Subject Probability for Poor Prognosis

Score	Cons	Coeff.	Y = -3.437 + 2.474 x score	P
0	-3.437	2.474	-3.437	0.180
1	-3.437	2.474	-0.963	0.724
2	-3.437	2.474	1.511	0.968

PROBABILITY FOR POOR PROGNOSIS CARD

Scoring Card for Severe Preeclampsia with gestational age <37 weeks
Patient Name :
Fill some with complete data. Provide a cross in the column corresponding to the patient's condition.

No		**Yes**	**No**	**Patient Score**
1	How old are you <20 year old or > 35 year old ?	1	0	
2	Is your gestational age 28-33 weeks ?	1	0	
	Total Score			

Based on total score, whether subject probability had poor prognosis. Provide a cross in the column corresponding to the patient's condition.

Score	**Probability Poor Prognosis (%)**
0	3.1%
1	27.6%
2	80.6%
Day/Date Prognosis made :	
Doctor	
Signature	

Table 7. Intersection

No	(+) if Greater Than or Equal To	Sens.	Specificity
1	-1.0000	1.000	.000
2	.5000	1.000	.444
3	1.5000	.538	.926
4	3.0000	.000	1.000

SCORING CARD FOR POOR PROGNOSIS

Scoring Card for Severe Preeclampsia on Gestational Age <37 weeks
Patient Name :
Fill some with complete data. Provide a cross in the column corresponding to the patient's condition

No		**Yes**	**No**	**Patient Score**
1	How old are you <20 year old or > 35 year old	1	0	
2	Is your gestational age 28-33 weeks	1	0	
	Total Score			

Subject had poor prognosis if score 2
Subject had good prognosis if score 0 - 1
Based on total score whether subject had good or poor prognosis?

Day/Date Prognosis made :
Doctor
Signature

Discussion

The present study was able to demonstrate that using multi-variate analyses, we were able to develop a predictive table and a scoring card that would help make diagnosing and risk factor assesment of potential pregnant patients with impeding pre-eclampsia easier, namely for the less experience healthcare providers. The data presented here were based on the 40 subjects recruited for our study which included pregnant women with severe preeclampsia. What was interesting to note is that in our analyses shows that there are no significant association between maternal age with the prognosis associated with severe preeclampsia. It is also worth noting that extreme maternal age is closely linked to an increased risk of preeclampsia in some studies. Research on the risk of preeclampsia during antenatal follow up consisting of 52 cohort and case control in other studies demosntrates that pregnant women over age 40 years had twice the risk of preeclampsia as compared with younger age patients (6). In addition, previous studies have shown that the risk of occurrence of pre-eclampsia will increase by 30% for every age since the age of 34 years (9). Another point worth mentioning is that in our study, primigravida and grand-multigravida had poor prognosis as compared with multigravida. Our further analyses also indicates that there is no significant relationship between the increase in gravida and poor prognosis in pre-eclampsia, provided they are not of the grand-multiparagravidarum group. The reason for the increased risk in primagradvida remains unknown, and has been desribed previously (10).

In contrary to common belief, our study demonstrated no significant relationship between a previous history of pre-eclampsia and that of the increased progrnosis of developing severe pre-eclampsia in future pregnancies. Previous studies have shown that the risk of developing pre-eclampsia can increase from 2.5% in women who had a single birth to 3.4% of pregnancies in multigravida pregnancies (10). A history of previous preeclampsia is a risk factor for the occurrence of preeclampsia in subsequent pregnancies. In fact, it has been mentioned that the incidence of preeclampsia are likely to be repeated up to twenty-fold in the next pregnancy compared with women without a history of pre-eclampsia (13). Duckitt and Harrington reported that there is a likelihood of up to seven times the incidence of pre-eclampsia in women with no history of pre-eclampsia as compared to women with no history of pre-eclampsia (6). The incidence of recurrence of pre-eclampsia is also dependent on how previous events occur, for example how the outcome of treatment and how easy it was to manage the condition previously, although the exact relationship does not appear to be clearly demonstrated (12). If pre-eclampsia occurs in pregnancy of less than 28 weeks, the risk that pre-eclampsia can develop in subsequent pregnancies is 38.6%. At 29-32 weeks of gestation, the risk of recurrence of pre-eclampsia was reported to be 29.1%. For pregnancies of 33-36 weeks of gestation, the risk of recurrence was 21.9% and in cases of pregnancy ≥ 37 weeks, the risk of recurrence was 12.9% (14). It also said that women with recurrent preeclampsia is often associated with the incidence of more severe preeclampsia as compared with women who previously experienced pre-eclampsia. They are predisposed to a number of high risk conditions which includes preterm labor, placenta and fetal death solution (13).

When looking into the gestational age and prognosis, our study suggests that there is a significant association between these two factors. Based on gestational age, pre-eclampsia can be categorized as the early onset preeclampsia (before 34 weeks gestation) or the late onset (≥ 34 weeks) (14). Early onset preeclampsia is associated with abnormal placentation and can be diagnosed based on the abnormal uterine artery found from using the Doppler examination. Another feature that is consistent with this condition is the stunted fetal growth and deterioration in the mother's health condition. In contrast to early pre-eclampsia, late pre-eclampsia is the result of maternal factors and rarely, other than symptomatic features that can be observed as a late stage presentation, this condition has no specific signs that can be used as an indicator such as those in early pre-eclampsia.

There are several limitations that is worth menitioning in this paper. To achieve a good analyses a much larger sample would be needed, employing mutlicentre cooperations and longer term follow ups. Such results would provide better representation and thus more meaningful data that could be sufficiently robust for healthcare providers to use as a "pre-clampsia score card". It needs to be reminded that the present study does provide a certain platform and justification for such a large scale study to be conducted in the nead future, and thus is of value at the present time. Another limitation is that the recruitment of subjects were restricted to patients without any other complications, which may not be reflective of the conditions being presented by many pre-eclamptic patients at the time of presentation. The reason for this was for us to have a restrive data which will provide lesser number of variables that could lead to increased variations in our predictive modelling. However, in doing so, this has lead to the possible limitation to the scoring system we developed, that is unable to be adapted into real life situation. This limitation needs to be overcome in future studies.

In conclusion, the present study was able to develop a scoring system which could assist healtcare providers in making a prediction of the outcome of pre-eclamptic patients, but needs to be validated in a more robust study due the present limitations. Our analyses demonstrates that maternal age and gestational age could be used as a predictor for the occurrence of clinical deterioration of severe preeclampsia In pregnant women with severe preeclampsia <37 weeks and therefore should be taken into consideration when applying to future studies.

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