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The Role of Soluble Fms-like Tyrosine Kinase 1 and Maternal Characteristics in Preeclampsia Scoring Card as a Predictor of Severe Preeclampsia

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Abstract
Preeclampsia is the leading cause of maternal mortality and morbidity worldwide. The capacity to predict maternal and neonatal outcome in pregnant women with preeclampsia remain immature although advanced have been made in obstetrics. Recent studies reported an antiangiogenic substance called *Soluble Fms-like Tyrosin Kinase-1* (sFlt-1) produced by the placenta of preeclampsia patients. It binds to *Vascular Endothelial Growth Factor* (VEGF) and *Placental Growth Factor* (PIGF) and act as a proangiogenic substance. The earliest period whereby sFlt-1 can be detected around 5 weeks prior to symptoms onset. This value increases dramatically as soon as symptoms arise. Whether sFlt-1 causes placentation problem or sFlt-1 is the result of placenta implantation defect is still unknown. This present study aimed at establishing a prognostic tool through sFlt-1 and maternal characteristics therefore reducing the rate of mortality in pregnant women with preeclampsia and aiding clinical assessments and interventions. In a nested case control study, 40 preeclampsia women diagnosed clinically were enrolled. By determining angiogenic factors and maternal characteristics were determined that could be used as a prognostic tool through logistic regression. In this study, the scoring card had good calibration and discrimination value with a p-value >0,05 and AUC 0.917 (95% CI 0.833 to 1.00). Respectively, subjects with total scores of 0, 1, 2, and 3 had 0.23%, 4.6%, 50.4%, and 95% chance of poor prognosis. Maternal age, gestational age, and levels of sFlt-1 appear to be strong predictors for poor clinical outcomes in patients with preeclampsia.
Keywords: Severe preeclampsia, clinical predictor, poor prognosis

1. Introduction

Pregnancy related complications causes maternal death worldwide every minute. An estimated 1.400 maternal deaths daily or over 500.000 maternal deaths resulted from obstetric complications (pregnancy, delivery and postpartum) (WHO/UNICEF/UNFPA 2000).

The maternal and infant mortality rates are also a major problem in Indonesia, according to the Indonesian Health Survey (Indonesian Ministry of Health, 2005). Maternal Mortality Rate (MMR) in Indonesia remains the highest amongst Asean countries, despite the reported Indonesian Demographic Health Surevy (IDHS) MMR decrease. MMR in Indonesia from 2003 through 2006 were 307, 270, 262, and 255 per 100,000 live births, respectively. This trend continued to decrease during 2010 where the maternal mortality rate was 220 deaths per 100,000 live births an the infant mortality rate was 27 deaths per 1,000 live births. These were still far from the targeted rates set by the Millenium Development Goals (MDGs) where the 2015 maternal mortality rate was 102 per 100,000 live births. There are several major causes of maternal death like haemorrhage, preeclampsia and hypertensive disorders of pregnancy, abortion complications, obstructed labour, and infections. In developing countries, however, the second leading cause of premature delivery and infant deaths resulted from preeclampsia. Worldwide, an estimated 5 to 7% preeclampsia cases were found; similarly 5-10% preeclampsia cases were found in Indonesia (Indonesian Ministry of Health, 2005).

According to the Cochrane Review, severe preeclampsia can occur prior to 34 weeks gestaional age. In addition, an estimated 50% of cases were delivered early within 24 hours of admission (Churchill & Duley 2007).

Despite management guidelines set by Advanded in Labour and Risk Management (ALARM) in 2010 to reduce morbidity and mortality, the greatest dilemma is between when deliver and balancing the risks before 34 weeks of pregnancy. Risk of multisystem organ failure for the mother by delaying delivery could occur. However, delivering a very premature baby could however cause respiratory distress syndrome. Cut off point for gestational age varies between centres, babies born before 28 weeks have a small survival rate, whereas after 34 weeks the survival rate increases. Definitive treatment for preeclampsia is delivery of the baby and placenta (ALARM 2010).

During pregnancy, the complication rate of preeclampsia was 3-5%. Disagreement between authors regarding the definitive treatment still exist, some regard delivery and some consider survival of the baby, disease progression and risk of multisystem organ failure (Sibai 2003; Dekker 2009). Furthermore, the debate

between intervention or conservative approach of severe preeclampsia should stop since conservative approach have better perinatal outcome (Sibai 2003; Dekker 2009).

Preeclampsia is a condition unique to human. The aetiology of preeclampsia is still unknown. Numerous studies have been conducted to link aetoiology to treatment. The treatment focuses more on preventing hypertension and pereeclampsia.

Pathogenesis of preeclampsia have been postulated in many studies, failure of placental angiogenesis and pseudo-vasculogenesis during placental development has been linked to the pathogenesis of preeclampsia related to other conditions such as intrauterine growth restriction and/or multiple organ failure of the mother (Noris *et al.* 2005).

Key to a successful human pregnancy is loss of smooth muscle and elastic lamina from the vessel wall as far as the inner third of the myometrium, termed physiological conversion of the maternal spiral arteries. It is associated with a 5-10 fold dilation. Common complications of pregnancies suh as early-onset preeclampsia and fetal growth restriction accompany failure of conversion. Oxidative stress as a result spontaneous vasoconstriction and ischaemia-reperfusion injury and failure of conversion usually accompany failure of conversion (Burton *et al.* 2009).

Recent studies reported an antiangiogenic substance called *Soluble fms Like Tyrosin Kinase-1* (sFlt-1) produced by the placenta of preeclampsia patients. It binds to *Vascular Endothelial Growth Factor* (VEGF) and *Placental Growth Factor* (PIGF) and act as a proangiogenic substance. The earliest period whereby sFlt-1 can be detected around 5 weeks prior to symptoms onset. This value increases dramatically as soon as symptoms arise (Walfrido 2009).

Whether sFlt-1 causes placentation problem or sFlt-1 is the result of placenta implantation defect is still unknown (Levine *et al.* 2004).

Progress of this disease must be halted by delivering the placenta and also the baby eventhough it is still preterm. This is done because of the etiological hypothesis of this disease is from placenta. As a result, preterm labor risk is increased as well as morbidity and mortality of the baby (Dekker 2009).

Controversies still surround preeclampsia management, whether to terminate pregnancy < 37 weeks gestational age or to postpone delivery until pregnancy > 37 weeks gestational age. Therefore the purpose of this study is to determine which risk factors can be a predictor to pending delivery until the fetus reaches term without any complications.

2. Methods

A Prospective Nested Case Control Study from September 2011 to August 2012 involving preeclampsia patients with intrauterine single gestation at 28-36 gestational weeks. The exclusion criteria for this study were patients with a history of diabetes mellitus and renal disorder. Gestational age was determined by last menstrual period and biparietal diameter / femur length determined by ultrasonography (Mindray DP-100 Plus). Preeclampsia diagnosis was established if subjects had blood pressure ≥ 160 mmHg systolic or 110 mmHg 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 (Jhonson Tausak). VEGF, PIGF, and sFlt-1 levels were processed in the laboratorium by taking maternal blood of about 9 cc. In order to participate in the study, a written informed consent was obtained from the subjects. The study was approved by the local ethical and research committee.

Inclusion criteria were every preelampsia patients (n=40) that were admitted, stabilized, evaluated, and planned to have expectant management. Immediate delivery were performed in twenty-eight patients (n=28) within 24 hours of being admitted. Before pregnancies were terminated, the patients were given corticosteroids. Expectant management were defined as conservative management without any complications (n=12) that warrant termination of pregnany. Expectant management was conducted through bed rest, hourly blood pressure monitoring and 4-hourly urine output monitoring. Repeatedly, the patients were questioned regarding symptoms such as headache headache, visual disturbances and right upper quadrant pain. Hemoglobin, haematocrite, platelet count, serum liver enzyme, ureum, creatinine, uric acid, lactate dehidrogenase, and coagulation profile were part of the blood tests. A target of mean arterial pressure decrease of < 20% were initiated with oral anti hypertension medication (nifedipine 30-120 mg/24h). Anti seizure mediation (magnesium sulfate) were given if needed. Fetal lung maturation using intramuscular dexamethasone was used. Fetal assessment was achieved through ultrasonography by estimating gestational age and amniotic fluid index. Fetal heart rate were measured per 15 minutes. Delivery were performed if no contraindication to expectant management existed or pregnancy has reached term. Fetal distress requiring observation were fetal indication for pregnancy termination. The attending physician were responsible for choosing the mode of delivery, based on the presenting obstetric and fetal indication.

Where appropriate, the data were presented as median or range. A chi square analysis (CI 95%) was analyzed for all variables, if p value was < 0,05 in bivariate analysis, a multivariate analysis was further

performed (backward and stepwise). A prognostic model were chosen based on calibration and discrimination tests. Scoring system were created through simulation by counting probability and cut off.

3. Results

Fourty subjects (n=40) who fulfilled our inclusion criteria were recruited for this study, whereby 28 patients (70%) had immediate delivery and the remaining 12 were managed expectantly. Gestation prolongation time vary between 24 hours and 171 hours. Intra uterine fetal death occurred in one patient that 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	Percentage
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		
Positive	6	15%
Negative	34	85%
Gravida		
Primi&Grande	14	35%
Multigravida	26	65%

The most age group was between 20-35 years old (65%). Thirty five percent of patients were primigravida and grand-multigravida, i.e. history of having more than 4 pregnancies. Previous history of preeclampsia was found only in 15% of the recruited subjects.

Result of laboratory assessment of antiangiogenic level and proangiogenic are shown in table 2.

Table 2. Result of laboratory assessment of antiangiogenic level and proangiogenic level in severe preeclampsia patient < 37 weeks gestational age (N=40)

Angiogenics Level (ρg/ml)	Mean ± SD	Median	Skewness	Range
sFlt-1	24,290.775 ±14,221.373	27,225.5	-0.32	559.0-42,280.8
PlGF	28.492 ± 26.20	16.7705	-1.522	2.2-110.9
VEGF	23.165 ± 54.99	8.5	5.114	2.5-335.4

Eligible variables for multivariate analysis (p<.25 based on bivariate analysis) were maternal age, gestational age, previous PE, level of sFlt-1, VEGF, and PlGF (table 3).

Table 3. Bivariate Analysis Result of All Variables with Prognosis in severe Preeclampsia < 37 weeks

Variable	Prognosis		Total	p value	OR	CI 95%
	Poor (< 24 jam)	Good (≥ 24 jam)				Min - Max
Maternal age						
20 - 35 yo	9 (22.5%)	17 (42.5%)	26 (65%)	0.101	0.4	0.87–13.239
<20 & >35 yo	9 (22.5%)	5 (12.5%)	14 (35%)			
Gestational age						
28 - 33	16 (40%)	7 (17.5%)	23 (54.5%)	<0.001	7.143	3.06 – 95.9
34 - 36	2(5%)	15 (37.5%)	17 (45.5%)			
slFt-1 level						
>24,290.775	15(37.5%)	7 (17.5%)	22 (55%)	0.002	10.714	2.32 –49.49
≤24,290.775	3 (7.5%)	15 (37.5%)	18 (45%)			
VEGF level						
<23,1695	18 (45%)	17 (42.5%)	35 (87.5%)	0.05	0.486	0.345 –0.683
≥23,1695	0 (0%)	5 (12.5%)	5 (12.5%)			
PlGF level						
<28,441	16 (40%)	9 (22.5%)	25 (62.5%)	0.003	11.556	2.115-63.127
≥28,441	2 (5%)	13 (32.5%)	15 (37.5%)			
Previous PE						
No	17(42.5%)	17 (42.5%)	34 (85%)	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%)	0.744	1.364	0.370– 5.028
Multigravida	11(27.5%)	15 (37.5%)	26 (65%)			

In order to develop a prognostic model using logistic regression (backward stepwise), all variables with p < 0.25 were included. Three variables were found to be significant (table 4).

Table 4. Backward stepwise

Variabel	B	S.E.	stat	p	OR	CI 95%	
						Min	Max
Maternal age	2.722	1.238	4.834	.028	15.207	1.344	172.087
Gestational Age	3.548	1.445	6.026	.014	34.751	2.045	590.593
sFlt-1 level	2.895	1.270	5.200	.023	18.092	1.502	217.933
Konstanta	-6.241	2.085	8.959	.003	.002		

Based on Hosmer Lemeshow test, this model was well calibrated with p value of > 0.05 (table 5).

Table 5. Hosmer and Lemeshow Test

Step	Chi-square	Df	Sig.
1	1.986	7	.961
2	4.073	7	.771
3	3.685	8	.884
4	1.833	5	.872

This model was also well discriminated based on the area under the curve of scoring model was 0.917 (95% CI 0.833 to 1.00).

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

Table 6. Subject Probability for Having Poor Prognosis

Patients Score	constanta	Coefficient	Y = (-6.049 + 3.033 x total score)	1 p= ---------- 1 + exp (-y)
0	-6.049	3.033	-6.049	0.0023
1	-6.049	3.033	-3.016	0.046
2	-6.049	3.033	0.017	0.504
3	-6.049	3.033	3.05	0.95

After the probability of poor prognosis were calculated, a scoring card that could be used in everyday practice were developed. At a score greater than 2, the sensitivity was 92.3% and specificity was 74.1%. From the table above, we also made a scoring card that could be used daily by healthcare providers.

Scoring Card for Severe Preeclampsia with Gestational Age <37 weeks

Patient's Name:

Fill this data completely. Cross in the column corresponding to the patient's condition.

No		Yes	No	Patient score
1	How old are you <20 yo or> 35 yo?	1	0	
2	Is your gestational age 28-33 weeks?	1	0	
3	is your sFlt-1 levels > 24290.7750 pg / ml?	1	0	
	Total score			

Based on the total score. what is the probability subject to the occurrence of a poor prognosis. Give a cross in the column corresponding to the patient's condition.

Score	Probability Poor Prognosis (%)
0	0.23%
1	4.6%
2	50.4%
3	95%

Day / date Prognosis made:
Physician:
Signature

Scoring Card for Severe Preeclampsia with Gestational Age <37 weeks

Patient's Name:

Fill this data completely. Cross in the column corresponding to the patient's condition.

No		Yes	No	Patient's score
1	How old are you <20 yo or> 35 yo?	1	0	
2	Is your gestational age 28-33 weeks?	1	0	
3	is your sFlt-1 levels > 24290.7750 pg / ml	1	0	
	Total Score			

Subject had poor prognosis if score 2-3
Subject had good prognosis if score 0-1
Based on the total score of the subject whether is good or poor prognosis?

Day / date Prognosis made:
Physician:
Signature

4. Discussion

Using multi-variate analysis, a predictive table and a scoring card that aid diagnosing and risk factor assessment of potential impending preeclampsia. Fourty severe preeclampsia pregnant patients were recruited for our study. This study found no significant association between maternal age with prognosis of severe preeclampsia. Furthermore, in some studies extreme maternal age is linked to an increased risk of preeclampsia. Research on preeclampsia risk on 52 cohort and and case control demonstrated that pregnant women over the age of 40 had twice the risk of preeclampsia as compared with younger patietnts (Dekker 2009). After the age of 34 years,

preeclampsia occurrence risk increase by 30% yearly (Levine *et al.* 2004). By comparing with multigravida, our study demonstrated that primigravida and grand-multigravida were associated with poor prognosis. Provided that the patients were not of the grand-multiparagravidarum group, no significant relationship exists between the increase in gravida and poor prognosis in preeclampsia. As it has been previously described, the cause of increasing risk in primigravida is still unknown (Trogstad & Stoltenberg 2011).

Contrary to popular belief, no significant relationship exist between previous history of preeclampsia and that of the increased prognosis of developing severe preeclampsia in future pregnancies. Risk of developing preeclampsia increases from 2.5% in women with single birth to 3.4% in multigravida pregnancies (Trogstad & Stoltenberg 2011). Risk factor for occurrence of preeclampsia is having a history of preeclampsia. This is further supported that preeclampsia incidence will be repeated twenty-fold in subsequent pregnancy (Odegard *et al.* 2000). Women with preeclampsia history have a 7 fold increase in incidence of preeclampsia (Duckitt & Harrington 2005). Recurrence of preeclampsia incidence depend on the mechanism of previous events, as an example outcome of treatment and ease of managing previous condition. When preelampsia occur in pregnancies less than 28 weeks, the risk of 38.6% preeclampsia can develop in future pregnancies. During gestational age of 29-32 weeks, preeclampsia recurrence was reported at 29.1%. During gestational age of 33-36 weeks, recurrence risk was 21.9%. Recurrence risk was 12.9% for gestational age of ≥ 37 weeks (Mostello *et al*. 2008). Women with recurrent preeclampsia is associated with the incidence of more severe preeclampsia when compared to women without previous preeclampsia. These women are at risk for high risk conditions that include preterm labor and placenta and fetal death solution (Hnat *et al*. 2002).

Significant association between gestational age and prognosis exist. Preeclampsia can be categorized as early onset (prior to 34 weeks gestation) or late onset (≥ 34 weeks) (Von Dadelzen *et al.* 2003). Through Doppler examination, early onset preeclampsia is associated with abnormal placentation. Furthermore, stunted fetal growth and deterioration in the mother's health status. Late preeclampsia, however, resulted from maternal factor, and rarely other than symptomatic features that can be observed as a late stage presentation. This is not associated with any specific signs which can be used as early preeclampsia indicator (Valensise *et al.* 2008).

Laboratory results of pregnant women with severe preeclampsia reported mean VEGF levels of 23.165 ± 54.99 with a range from 2.5 to 335.4 pg/ml. A chi-square test with a p value = 0.05 indicate that there is a significant relationship between VEGF levels and prognosis of severe preeclampsia. With regard to this study, VEGF levels can be used as a predictor of preeclampsia severity despite only having five patients with the highest score of 335.4 pg/ml and the lowest score of 2.5 pg/ml. According to PurwounuY, preeclamptic mothers had an average VEGF level of 37.7 ± 3.8 pg/ml. This study, however had a mean of 23.165 ± 54.99 pg / ml (Purwosunu *et al.* 2009).

VEGF expression was induced rapidly and reversibly by hypoxia through transcription an stabilization of mRNA (Lickens *et al.* 2001). Furthermore, PIGF is also secreted when hypoxia is present. The role of hypoxia is not known clearly in the regulation of PIGF. Usually, absence of hypoxia could lead to VEGF gene transcription and mRNA degradation and the protein it produces (De Falco 2012; Nagy *et al.* 2003).

Research by Buhimschi on sFlt-1, VEGF, and PIGF excretion in women with severe preelampsia during appearance of clinical manifestations. It is found that excretion of angiogenic factors VEGF are increased in severe preeclampsia and reflect two separate phenomena with an additional effect, namely the production of endogenous renal and glomerular leakage (Buhumschi *et al.* 2006).

PIGF levels was 28.492 ± 26.20 with a range from 2.2 to 110.9 were found. Statistical test with chi-square, with a p value < 0.05 indicated significant correlation between PIGF levels and severe PE prognosis. With regard to this study, PIGF can be used as a predictor for clinical deterioration in preeclampsia less than 37 weeks gestational age.

In the third trimester of preeclampsia, it was found that PIGF levels was 90.7 (45.3 to 706) pg / ml (De Vivo *et al.* 2008). This study however had a lower level of PIGF of 28.492 ± 26.20 pg / ml. As previously mentioned, hypoxia induces PIGF secretion, but the role of hypoxia on PIGF regulation is still not clearly known (19). In several studies however concluded that VEGF and PIGFlevels were decreased in severe preeclampsia patients (Nishimoto *et al.* 2009; Widmer *et al.* 2007).

ean levels of sFlt-1 is 24,290.775 ± 14,221.37 ρg / ml with a range from 559.0 to 42,280.8. Statistical test with chi square p value < 0.05 suggests that there is a significant association between levels slFt-1 and prognosis in severe preeclampsia <37 weeks. In severe preeclampsia, sFlt-1 will be increased in the placenta and the maternal blood (Maynard *et al.* 2003). A higher level in early onset severe preeclampsia is found compared with late onset and is opposite to the circulating levels of free PlGF in circulation. Here PlGF levels will be reduced in patients with severe preeclampsia (18,25). Stepan (2007), in his research found that the levels of sFlt-1 in preeclampsia in third trimester is 1,403.6 ± 555 pg / ml (Stepan *et al.* 2007).

McElrath (2012), in a study comparing normal pregnancy, gestational hypertension, and preeclampsia found that at 35 weeks of gestation in normal pregnant PlGF level was 385.6 (175.2 to 750.8), the levels of gestational hypertension was 256.9 (134.0 to 552.5) and in patients with preeclampsia the levels are 134.965 to

308.5, while the levels of sFlt - 1 in normal pregnancy was 9.7 (6.7 to 14.6), gestational hypertension was 11.0 (6.7 to 16.6) and preeclampsia was 18.4 (10.4 to 32.0). PlGF/sFlt-1 ratio in normal pregnancy was 42.0 (14.9 to 98.6), the ratio PlGF/sFlt-1 on gestational hypertension was 26.1 (8.7 to 68.7) and the ratio of PlGF/sFlt -1 in preeclampsia was 7.6 (2.7 to 30.1). AUC (95 % CI) for PlGF was 0.72 (0.67 to 0.77) the optimal cut off was ≤ 242.67 with 67.8% sensitivity and 64.8 % specificity, and positive predictive value of 10.4%, negative predictive value of 97.1 %. SFlt-1 AUC (95 % CI) was 0,72 (0.67 to 0.77) the optimal cutoff ≤13.12 with a sensitivity of 62.7% and specificity 68.9%, positive predictive value 10.9% and the value of 96.8 % negative predictive. PlGF/sFlt-1 AUC ratio of 0.74 (0.69-0.79) with the optimal cut off ≤14.42 with a sensitivity of 61.0% and specificity 75.1%, positive predictive value 13.0% and the predictive value negative 97.0% (McElrath *et al.* 2012).

Verlohren (2012), states that the ratio sFlt-1/PlGF enable identification of pregnant women with severe preeclampsia at risk for immediate performed labor. It is a reliable tool to distinguish different types of hypertensive disorders associated with pregnancy. However, preterm birth may increase the risk of perinatal morbidity. In addition, maternal complications which can also be found in the case of late preeclampsia. Identification of patients with preeclampsia is very important because an intensive monitoring and referral to specialized perinatal care center can essentially reduce morbidity in the mother and fetus. Various case-control study in addition to this prospective study was to explain the role of measurement sFlt-1/PlGF in the peripheral blood of pregnant women as a diagnostic tool. The results demonstrated that the increase in the ratio of sFlt - 1 and PlGF below the cut point value 85, as judged by Elecys, allows the determination of clinical PE. They analyzed the remaining time to do deliveries in 164 patients with PE / HELLP within 2 days or less, 2-7 days, and more than 7 days. In the group with gestational age < 34 weeks (69 of 164 patients), the mean ratio sFlt-1/PlGF in patients who delivered within 2 days was 616.42 ± 81.15. Patients who delivered within 2-7 days with the ratio found sFlt-1 / PlGF 547.93 ± 98.39. However, patients who delivered more than 7 days met with a ratio sFlt / PlGF 225.55 ± 60.59. At ≥ 34 weeks of gestation group with PE / HELLP is to deliver within 2 days sFlt1/PlGF found with a mean ratio of 190.02 ± 23.11. Patients who delivered within 2-7 days sFlt-1/PlGF found with a mean ratio of 146.03 ± 24.28. However, pregnant patients > 7 days sFlt-1/PlGF found with a mean ratio of 60.47 ± 21.89. An important finding in this study were patients with severe PE / HELLP with high ratios of sFlt-1/PlGF had a significantly increased risk for labor performed immediately. Patients who gave birth within 7 days sFlt-1/PlGF ratios are found to be significantly higher compared to patients who delivered > 7 days . This also applies to the group of patients with a gestational age < 34 weeks and ≥ 34 weeks at the top. So the ratio of sFlt-1/PlGF is a relevant prognostic factor for having a baby soon in patients with severe preeclampsia / HELLP (Verlohren *et al.* 2012).

In this study if we do multivariate analysis, maternal age, gestational age, and levels of sFlt-1 include into the scoring card. So we see here that although individually the levels of VEGF and PlGF statistically significant association with clinical deterioration, but once entered into the multivariate analysis of the Backward and Stepwise VEGF and PlGF levels can not enter into the scoring card. Similarly, maternal age by itself has been without a significant relationship with clinical deterioration with $p > 0.05$ but when taken together with the other five variables included in the multivariate analysis and Stepwise Backward can finally get into the scoring card model. The model of the card contains the variables maternal age, gestational age, and levels of sFlt-1 have good value discrimination from the AUC value of 0.917 (95 % CI 0.833 to 1.00).

Several limitations are worth mentioning in this paper. In order 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-ecalmpsia 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 near 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 restricted 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 preeclamptic patients, but needs to be validated in a more robust study due the present limitations. Our analyses demonstrates that maternal age, gestational age, and level of sFlt-1 could be used as a predictor for the occurrence of clinical deterioration of pregnant women with severe preeclampsia <37 weeks and therefore should be taken into consideration when applying to future studies.

Research on predictors of clinical deterioration of the maternal and neonatal can further involve other angiogenic factors, and at different levels of hypertension in pregnancy such as chronic hypertension, mild preeclampsia, severe preeclampsia and eclampsia.

5. Conclusion

In this study, card making and probability scoring models are the result of clinical deterioration consists of: maternal age, gestational age, and levels of sFlt-1. Scoring card model includes maternal age, gestational age, levels of sFlt-1 may possess a good calibration value for p> 0.05. Discrimination is also good value that can be seen from the value of AUC 0.917 (95% CI 0.833 to 1.00). Subjects with total scores of 0, 1, 2, and 3 had 0.23%, 4.6%, 50.4%, and 95% poor prognosis, respectively.

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