Does proteinura in preeclampsia have enough value to predict pregnancy outcome?

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Summary

Objective: Preeclampsia is defined by the new onset of elevated blood pressure and protienuria after 20 weeks of gestation. Protienuria is one of the essential criteria for the clinical definition of preeclampsia. The authors investigated the predictive value of proteinuria in the outcome of pregnancies with preeclampsia. *Materials and Methods:* In this retrospective cohort study, they entered all pregnant women who were admitted with diagnosis of preeclampsia in Yahyanejad Hospital from 1998 to 2008. Patients' data such as age, gestational age, level of 24-hour urine protein, liver enzyme, blood urea nitrogen (BUN), creatinine, and other laboratory test. Also, prenatal and maternal outcome were studied. The data analyzed and compare with each other. *Results:* Out of 289 patients, 5.9% (17) women had placental abruption, 13.1 % (28) patients had intrauterine growth retardation (IUGR), 32.2% (96) had respiratory distress, and 26.6% (77) of the patients' infants were transferred to neonatal intensive care unit (NICU). Although the present study showed proteinurea cannot be a sufficient predictor for adverse consequences of preeclampsia, however, the incidence of pregnancy adverse effects increased in the patients with elevated 24-hour proteinuria. *Conclusion:* The authors concluded that proteinuria in patients with preeclampsia is associated with adverse outcome in pregnancy, although it is not an adequate predictor.

Key words: Preeclampsia; Proteinuria; Pregnancy outcome; Hypertention.

Introduction

Among hypertensive disorders in pregnancy, preeclampsia is known as a major cause of maternal and fetal mortality. Preeclampsia is referred to hypertension with proteinuria occurring after 20 th week of pregnancy in a woman with a normal blood pressure [1]. Clinical symptoms of preeclampsia usually occur at any time after the second trimester. Preeclampsia occurs in about 3.9 percent of pregnancies worldwide [2] and is defined as a particular pregnancy syndrome which can generally affect the whole body systems. The disease occurs in multiple organs such as kidneys, liver, and also brain and causes constant adverse effects [3]. The combination of proteinuria and hypertension is associated with adverse outcomes of pregnancy such as low neonatal consciousness at birth, intrauterine fetal death (IUFD), low birth weight (LBW), intrauterine growth restriction (IUGR) requiring admittance to neonatal intensive care unit (NICU). [4]. Gestational high blood pressure may be misleading because mild disease could quickly become severe [1]. Proteinuria is considered in the diagnosis of preeclampsia –eclampsia. These symptoms may appeared with a delay. Although, some women may have suffered the seizure before the onset of proteinuria, or mandatory delivery due to preeclampsia, however 17% of patients with eclampsia, did not have proteinuria at the time of the seizure [5].

Proteinuria is an important criterion for preeclampsia and is a specific test to assess severity of the disease and predict the consequences in the women suffering from preeclampsia [6] Proteinuria in preeclampsia occurs following damage to the glomeruli of renal endothelium. Impaired placental blood flow causes less perfusion and hypoxia, and ultimately leads to the release of placental debris and causes a systemic inflammatory response [7-8]. The coherence between proteinuria and adverse fetal outcomes were first considered first by Page and Christanson [9]. Later, other studies showed that the increased protein excretion in women with preeclampsia was associated with fetal and maternal adverse outcomes [10, 11]. However, these initial studies, not only lacked the adequate sample size, but also the numbers which were presented as the cutoff points of urinary protein levels, demonstrated clear discrepancies.

A group of researchers in the United States reported that about 16% out of 3,201 maternal deaths were owing to high blood pressure consequences in pregnancy. It is necessary to say that they reported later more than half of these deaths were preventable [12, 13].

Some investigators have evaluated microalbuminuria as a potential predictive test for preeclampsia. Sensitivity fluctuated from seven to 90% and specificity from 29% to 97%, respectively. It indicated a low clinical predictive value [7]. Newman *et al*. admitted 209 patients with a diagnosis of pre-eclampsia, of which 125 women had proteinuria less than five g/h, 43 women had five to ten g/h, and 41 women had more than ten g/h. No significant dif-

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ferences of the maternal and fetal complications were observed between the three groups [14]. Also, Thangaratinam *et al.* studied the maternal complications in the three-point cut-off of proteinuria at two, five, and ten g. The results defined proteinuria as a poor predictor of maternal and fetal complications in the women with preeclampsia [6]. Although, Gangaram *et al.* in their study on 163 women with hypertension during pregnancy, concluded the consequences are more intense when proteinuria is associated with hypertension [15]. A review article by Lindheimer *et al.* suggested evaluating physiologic kidney function in protein excretion is necessary for proteinuria assessment. Also, cutoff point for abnormal proteinuria was only used to diagnose pre-eclampsia and not as guidance for management of disease [7]. The aim of this study was to identify the predictive value of proteinuria in pregnancy outcome with preeclampsia.

Materials and Methods

In this retrospective cohort study, all patients admitted with the diagnosis of preeclampsia and eclampsia in Yahyanegad Hospital in Babol (north of Iran) from 2000 to 2010, were entered in the study.

Exclusion criteria consisted in patients with kidney disease, those with background of hypertension, and chronic proteinuria.

The definition of preeclampsia according to the National High Blood Pressure Education Program (NHBPEP) Working Group was used [16]. Preeclampsia was defined as systolic pressure 140 mmHg and/or diastolic pressure 90 mmHg on two occasions, at least six hours apart, and proteinuria with a urinary total protein of 300 mg/24 hours in a single specimen occurring for the first time in the second half of pregnancy [17]. All pregnant women with above criteria were included.

Maternal age, gestational age, parity, clinical symptoms (headache, blurred vision, epigastric pain, oliguria), laboratory findings (complete blood count (CBC), platelet, liver function tests, BUN, creatinine (CR), protein 24 hours), maternal complications (pulmonary edema, kidney damage, blood transfusion, liver complications, transfer to the ICU, incidence of caesarean section, maternal mortality), and prenatal complications (preterm labor, placenta abruption, IUGR, fetal death, fetal distress, Apgar scores [16] at five minutes were recorded. Significant difference was considered at $p \leq 0.05$.

Patients were divided into two groups: Group A: patients with gestational hypertension and proteinuria. Group B: patients with gestational hypertension and proteinuria and changes in clinical findings. Outcome of pregnancy in each group was compared with the other groups after entering the data obtained through the patients' files. To calculate, SPSS 16 software was applied. The tests which were used to analyze included ROC curve, T test, and Chi Square.

Results

Over ten years, 570 patients were admitted with preeclampsia in the present hospital. According to inclusion and exclusion criteria, 289 patients remained in the study and were evaluated. Their mean age was 29.46 ± 7.43 years.

In 5.9% of patients (17), the placental abruption occurred. The mean 24-hour urine protein was significantly higher in the patients with placental abruption (p =0.000, Table 1)

IUGR occurred in 13.1% of patients (38). In these patients, mean 24-hour urine protein was higher than the patients who had not IUGR (p =0.000, Table 1). The respiratory distress syndrome (RDS) observed in neonates of 33.2% patients (96) and infants of 26.6% patients (77) were transferred to the NICU. Both of these patients had 24-hour urine protein levels higher than other patients (in both cases p =0.000, Table 1).

Using ROC curve, the cutoff points for 24-hour urine protein was 1,250 mg in RDS (Figure 1), 1,750 mg in the placental abruption (Figure 2), 1,650 mg in IUGR (Figure 3), and for transfer to the NICU 1,350 mg (Figure 4) were calculated. The sensitivity and specificity of three cutoff points for each outcome show to be correlated with the ROC curve in Table 2.

Tables 3-6 show the correlation between 24-hour proteinuria with the number of women with the pregnancy complications.

Mean 24-hour urine protein was significantly greater in patients with complications in the selective cutoff points.

Out of 289 patients, 207 patients had only proteinuria and categorized in group A. Eighty-two patients had other abnormal tests in addition to proteinuria and were categorized in group B. The mean age of patients in group A was 28.61 ± 6.32 years and 31.53 ± 7.27 in group B (p = 0. 329).

Table 1 – *Twnty-four hour urine proteinuria in patients with or without pregnancy outcome.*

p value	n. (%)		
0.00	17 (5.9)	yes	Placental
	272 (94.1)	no	abruption
0.00	38 (13.1)	yes	IUGR
	251 (86.9)	no	
0.00	96 (33.2)	yes	Respiratory
	193 (66.8)	no	distress
0.00	77 (26.6)	yes	Transfer to
	212 (73.4)	no	NICU

Table 2 – *Sensitivity and specificity of calculated cutoff points for 24-hour protein in predicting pregnancy complications.*

Pregnancy complication	Cutoff point	Sensitivity	Specificity	Roc curve	*p* value
Respiratory distress	1,250	91.7	78.4	0.857	0.000
Placental abruption	1,750	94.1	63.7	0.777	0.009
IUGR	1,650	88.9	64.5	0.793	0.000
Transfer to NICU	1,350	98.7	69.8	0.914	0.000

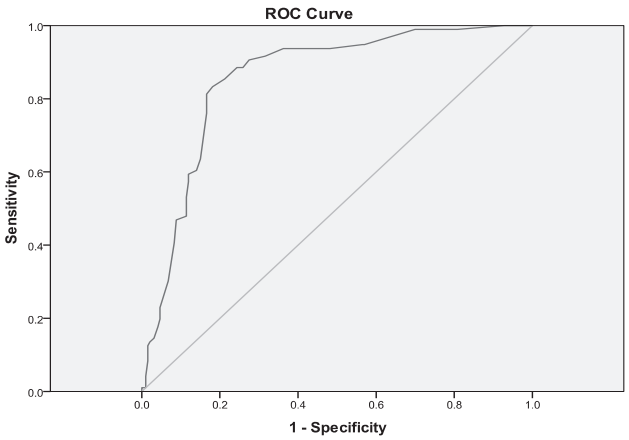

Figure 1 – ROC curve of comparison of 24-hour urine protein or respiratory distress.

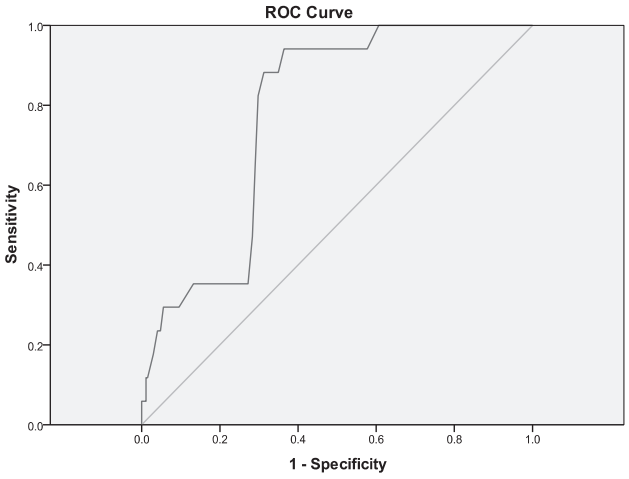

Figure 2 – ROC curve of comparison of urine protein 24 hr or placenta abruption

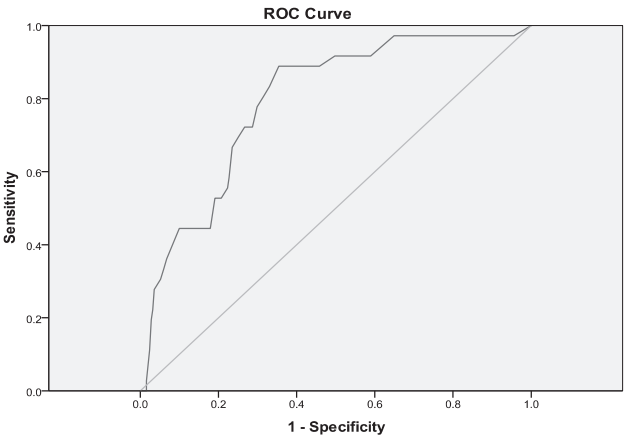

Figure 3 – ROC curve of comparison of 24-hour urine protein intrauterine growth retardation (IUGR).

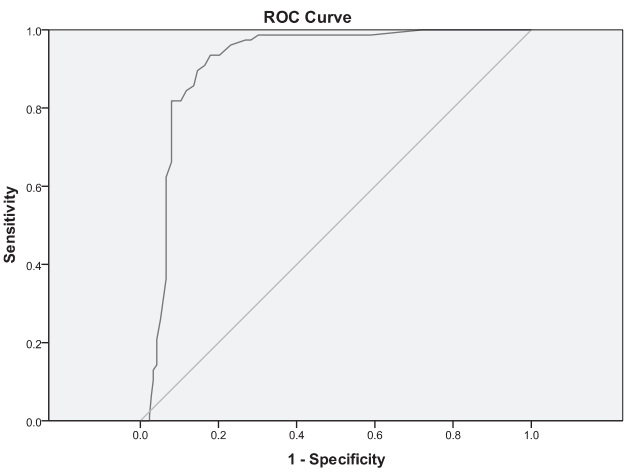

Figure 4 – ROC curve of comparison of 24-hour urine protein neonatal intensive care unit (NICU).

Table 3 – *Relationship of 24-hour protein according to determined cutoff points or respiratory distress.*

		Level of urine protein 24 hr	
		≤ 1,250	> 1,250
		N (%)	N (%)
Respiratory distress	Yes	8 (8.3)	91.7 (88)
	No	132 (68.4)	61 (31.6)

$p = 0.001$

Table 4 – *Relationship of 24-hour protein according to determined cutoff points or abruption placenta-*

		Level of urine protein 24 hr	
		≤ 1650	>1650
		N (%)	N (%)
Abruption placenta	Yes	1(0.6)	16 (94.1)
	No	173 (63.3)	99 (36.4)

$p = 0.000$

Table 5 – *Relationship of protein 24 hr according to determined cutoff points or IUGR*

		Level of urine protein 24 hr	
		≤ 1650	>1650
		N (%)	N (%)
IUGR	Yes	5 (2.9)	162 (97.1)
	No	33 (27.1)	89 (72.9)

$p = 0.000$

Table 6 – *Relationship of 24-hour protein according to determined cutoff points or transfer to NICU.*

		Level of urine protein 24 hr	
		≤ 1350	> 1350
		N (%)	N (%)
Transfer to NICU	Yes	1 (1.3)	76 (98.7)
	No	148 (69.8)	64 (30.2)

$p = 0.001$

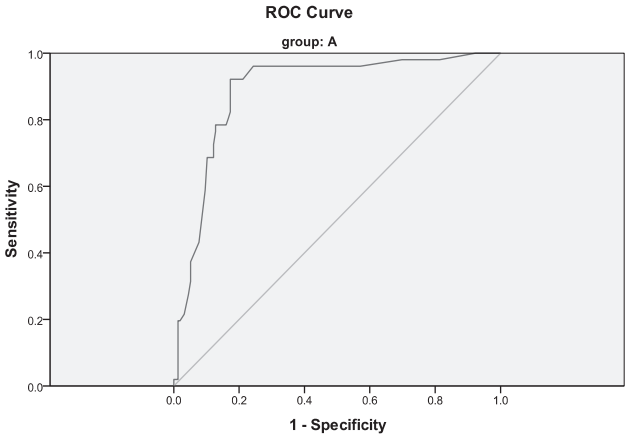

Figure 5 – ROC curve of comparison of 24-hour urine protein or respiratory distress in group A.

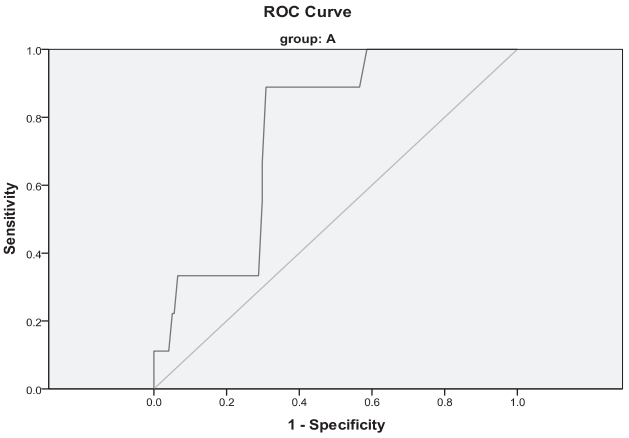

Figure 7 – ROC curve of comparison of 24-hour urine protein or abrubsion placenta in the group A.

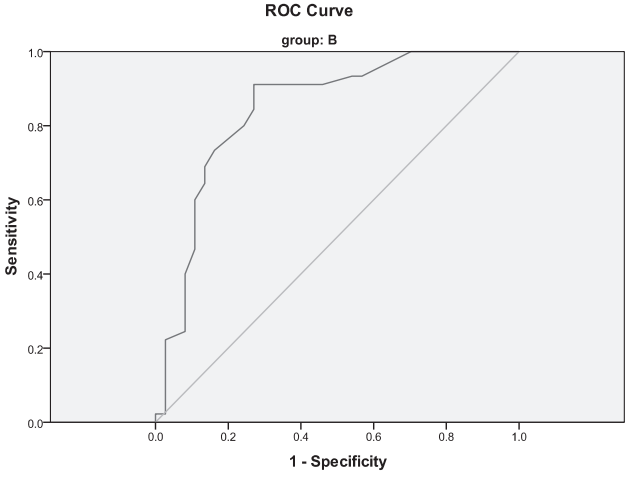

Figure 6 – ROC curve of comparison of 24-hour urine protein or respiratory distress in the group B.

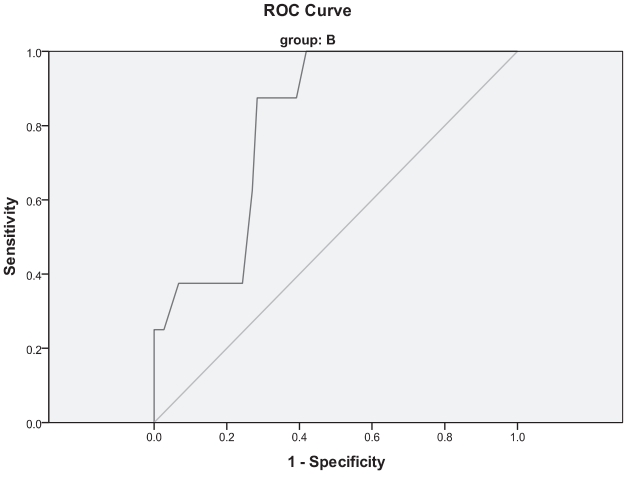

Figure 8 – ROC curve of comparison of 24-hour urine protein or placental abruption in the group B.

Blood transfusion in the whole samples were five patients: two patients in group A and three in group B. Total rate of injected platelets was reported in for patients which were all in group B. The number of IUFD was seven: five belonged to group A and two to group B.

Of 289 deliveries, 97.2% (281) cases were cesarean section and 2.8% (eight) had vaginal delivery: six normal deliveries belonged to group A and two deliveries to group B.

Other complications of groups A and B have shown to compare in Table 7. As can be seen, differences were all significant except in placental abruption.

Using ROC Curve, cutoff point for 24-hour urine protein which occurring in the respiratory distress in group A was 1,550 mg (Figure 5) and 1,150 mg in group B (Figure 6).

The cutoff point of 24-hour urine protein for the placental abruption in group A was 2,050 mg (Figure 7) and 2,150 mg in group B (Figure 8).

In the IUGR, cutoff point for 24-hour urine protein levels in group A and group B were 2,350 mg (Figure 9) and 1,650 mg (Figure 10), respectively.

Also, cutoff points of 24-hour urine protein for infants transferred to NICU in group A and group B were 1,850 mg (Figure 11) and 1,350 mg (Figure 12), respectively.

Sensitivity and specificity of calculated three cutoff points for each outcome and also, areas under the curve are shown according to each group in Table 8.

Discussion

Until now, the disorders of proteinuria in pregnancy have been considered as one of the most interesting challenges in obstetrics. The present study found the maternal adverse effect occurred when mean urinary protein was higher. Brown *et al.* as in the present study showed that maternal

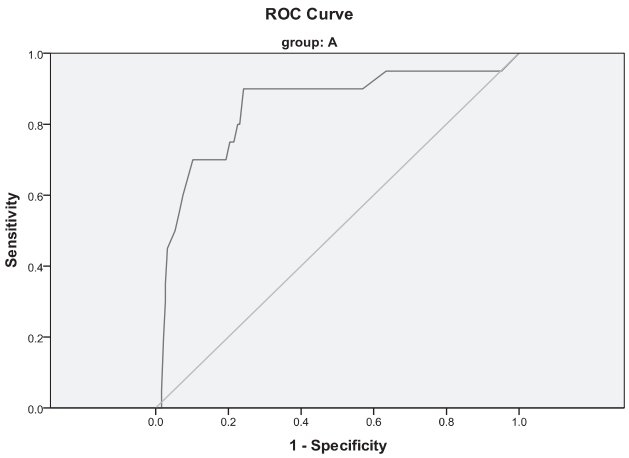

Figure 9 – ROC curve of comparison of 24-hour urine protein or intrauterine growth retardation (IUGR) in group A.

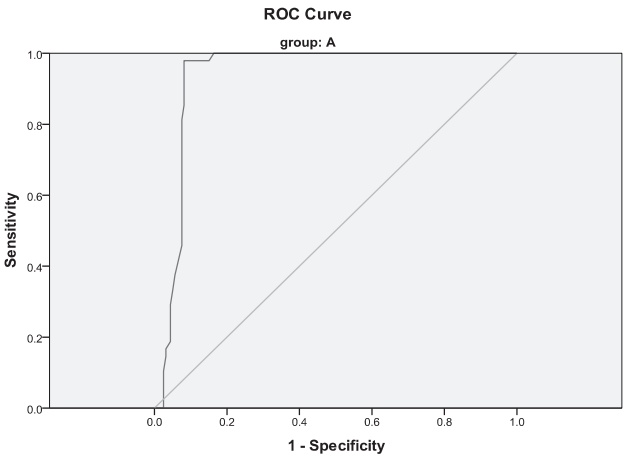

Figure 11 – ROC curve of comparison of 24-hour urine protein or transfer to neonatal intensive care unit (NICU).

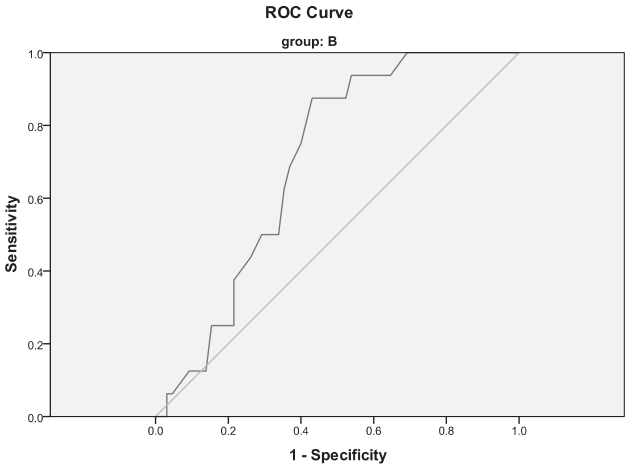

Figure 10 – ROC curve of comparison of 24-hour urine protein or intrauterine growth retardation (IUGR) in group B.

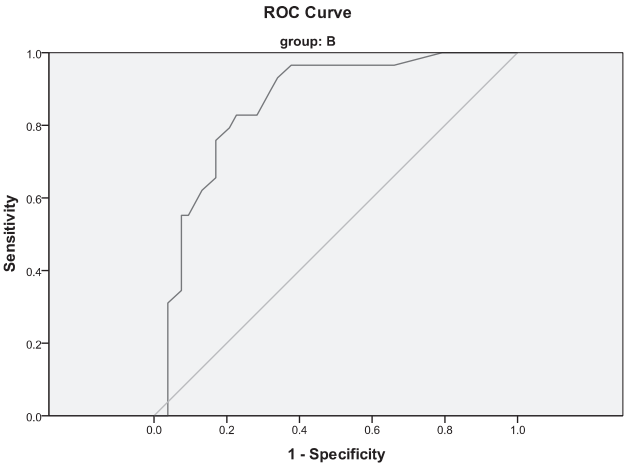

Figure 12 – ROC curve of comparison of 24-hour urine protein or transfer to neonatal intensive care unit (NICU).

proteinuria can be a good predictor [17]. Ferrazzani *et al.*, Gangaram *et al.,* and Chan *et al*. also showed a higher rate of complications when hypertension is associated with proteinuria [15, 18].

There are many conflicting results in the present study. In Thangarayinam, Newman, Nisell, Chua, and Schiff researches proteinuria is not a good predictor for maternal complications [6, 14, 19, 20, 21].

In this study, the authors found the cutoff points of 24-hour urine protein for each adverse outcome: 1,250 mg for RDS, 1,650 mg for IUGR, 1,750 mg for abruption placenta, and 1,350 mg requiring NICU.

Increased of adverse maternal outcomes occurred with a high cutoff point urine protein/creatinine ratio in preeclamptic women at greater than nine g/day, or greater than five g/day in women over 35 years [18]. However, Chua *et al.* studied the women with proteinuria over five grams with no significant increase was observed in the complications when their delivery delayed [20]. Newman *et al.* divided patients into three groups of proteinuria: less than five grams, five to ten grams, and over ten grams No significant differences were seen in complications between the three groups [14].

Thangaratinam *et al.* reviewed 16 articles from years 1951-2007. They evaluated cutoff points ten grams and five grams and increase of protein levels of two grams between the two measurement and determined likelihood ratios (LRs) for positive LR + and negative LR- test results in each of the points, although, they concluded proteinuria is a weak predictive for adverse consequences [6].

In the present authors' further research, they divided the patients into two groups: A and B. Regarding less rate and lower cutoff point of complications in group B vs group A, showed that proteinuria alone cannot be sufficient to predict all adverse consequences.

Table 7 – *Comparison of pregnancy complications in the groups.*

Complication		Group A N (%)	Group B N (%)	*p* value
Abruption placenta	Yes	9 (4.3)	8 (9.8)	0.096
	No	198 (95.7)	74 (90.2)	
IUGR	Yes	20 (9.7)	16 (19.8)	0.029
	No	186 (90.3)	65 (80.2)	
Respiratory distress	Yes	51 (24.6)	45 (54.9)	0.000
	No	156 (75.4)	37 (45.1)	
Transfer to NICU	Yes	48 (23.2)	29 (35.4)	0.039
	No	159 (76.8)	53 (64.6)	
IUFD	Yes	5 (2.4)	2 (2.4)	1.000
	No	202 (97.6)	80 (97.6)	

Table 8 – *Sensitivity and specificity of calculated cutoff points for 24-hour protein in predicting pregnancy outcome.*

Pregnancy complication	Group	Cut of point	Sensitivity	Specificity	Roc curve	*p* value
Respiratory distress	A	1550	96.1	75.6	0.889	0.000
	B	1150	91.1	73	0.846	0.000
Placental abruption	A	2050	88.9	69.2	0.759	0.009
	B	2150	87.5	71.6	0.810	0.004
IUGR	A	2350	90	75.8	0.849	0.000
	B	1650	87.5	56.9	0.700	0.014
Transfer to NICU	A	1850	100	83.6	0.937	0.000
	B	1350	96.6	62.3	0.857	0.000

Perhaps Lindheimer's findings are near to truth that suggested that blood pressure, evidence of liver damage, blood system, and nervous signs are reliable determinants in the severity of preeclampsia [7]. The present authors suggest a whole aspect study to evaluate proteinuria correlation with each of pregnancy consequences.

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