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D. DIMER TEST IN SEVERE VERSUS MILD PREECLAMPSIA

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Abstract:

Background: D.Dimer, is a by-product of blood clotting, has been linked to pregnancy-associated issues like gestational diabetes, premature rupture of membranes, and preeclampsia.

Aim of the study: To determine the D.Dimer levels in women with severe and mild preeclampsia and to correlate its level with severity of preeclampsia and to find out the cutoff points of D.Dimer for preeclampsia.

Patients and Methods: A hospital-based case-control research was conducted from January 1st to September 1st, 2023, on 150 pregnant women diagnosed with preeclampsia at the Duhok Obstetrics and Gynecology teaching hospital in Kurdistan, Iraq. The study divided the women into three groups: severe, mild, and normotensive, and estimated D.Dimer levels before labor.

Results: There was an escalated of mean D.dimer level of 1389.20±754.6 in the control group to 2097.7±229.59 in mild PE and 5429.52±757.11 in severe PE groups. The mean difference between mean D.dimer levels in severe preeclampsia, mild preecalmpsia and normotensive groups were statistically significant. Area under the Curve for the cut-off points for serum D.Dimer level revealed that the D.Dimer had an excellent area under the curve (0.932) which was statistically significant. Cut-off points, sensitivity, specificity, positive predictive value, and negative predictive value for D.Dimer demonstrated that 2500.0 point had the highest sensitivity and specificity to differentiate severe versus mild preeclampsia.

Conclusions: A significant association between pre-eclampsia and high D.Dimer levels in pregnant women may contribute to future risk of VTE

Keywords: D. Dimer Test, Mild Preeclampsia, Severe Preeclampsia.

Introduction

Preeclampsia is a hypertensive pregnancy disorder causing 2%-8% of pregnancy-related complications worldwide and 9%-26% of maternal deaths in low-income and high-income countries, presenting in near-term pregnancies [(1)]. Pre-eclampsia risk factors include family history, genetic predisposition, sexual cohabitation duration, maternal smoking, pregnancies, maternal age, in vitro fertilization, pre-existing conditions, increased placental mass, and trisomy 13 [(2)].

Preeclampsia, also known as proteinuria and hypertension, is a condition characterized by gestational hypertension of 140/90 mmHg on two separate occasions, accompanied by significant proteinuria of >30 mgs/mmol, arising de novo after the 20th week of gestation in a normotensive woman. Severe preeclampsia includes new onset hypertension, proteinuria, other maternal organ dysfunction, neurological complications, haematological complications, and uteroplacental dysfunction [(3)].

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Preeclampsia, a condition affecting the fetus, can be a single condition or include subtypes with different causes and clinical presentations. Its pathogenesis is divided into two stages: early stages, which involve altered placental development, and the second stage, which leads to acute maternal syndrome and systemic multi-organ dysfunction. The disease's underlying mechanisms are believed to be impaired placentation [(4)].

New hypertension after 20 weeks gestation should be assessed for preeclampsia symptoms. Blood pressure should be measured twice with four hours apart, and high-risk women should be monitored more frequently. Proteinuria can be detected using dipstick testing or spot urine albumin to creatinine ratios. Laboratory tests, such as PlGF or sFlt-1:PlGF ratio testing, are recommended for preeclampsia diagnosis in specific circumstances. High circulating angiogenic factors, such as sFlt-1 and PlGF, play a role in preeclampsia pathogenesis [(5, 6)].

The ACOG committee opinion, issued in 2015 and reaffirmed in 2017, does not recommend screening for preeclampsia, unless a medical history is obtained. D-dimer, a by-product of blood clotting and break-down, can detect pulmonary embolism, deep vein thrombosis, or disseminated intravascular coagulation. Interfering factors include pregnancy, malignancy, smoking, trauma, infection, or sepsis. D-dimer concentrations increase physiologically during pregnancy without thromboembolic complications [(7, 8)].

The coagulation-fibrinolytic system is significantly affected in preeclampsia patients due to maternal inflammatory reactions and dysfunction. D-Dimer testing is used to diagnose deep venous thrombosis (DVT), pulmonary embolism (PE), or disseminated intravascular coagulation (DIC) [(9)]. Studies have shown increased D-Dimer levels in preeclampsia compared to normotensive pregnant subjects. Higher D-Dimer levels indicate the presence of high levels of thrombus in blood, which explains the mechanism of damage in preeclampsia, where the dissolution of fibrin clot plays a vital role in endothelial damage [(9, 10)]. The deposition of fibrin in microvasculature, resulting in placental perfusion insufficiency, intrauterine fetal growth retardation, and dysfunction of some maternal organs. The smallest fragment of D-Dimer, resistant to plasmin degradation, reflects both fibrin polymerization and breakdown [(11, 12)].

Aim of the study: To determine the D.Dimer levels in women with severe and mild preeclampsia and to correlate its level with severity of preeclampsia and to find out the cutoff points of D.Dimer for preeclampsia.

Patients and Methods:

A hospital based case-control study conducted at outpatients clinic of Duhok Obstetrics and Gynecology Teaching Hospital, Duhok city, Kurdistan region, Iraq. A convenient sample size of 150 was used and the data collection was carried out over 9 month's period starting from 1st of January to 1st of September 2023. The sample was divided in to 3 groups; control, mild and severe preeclampsia with fifty women in each group. Informed verbal agreement from the participants before enrollment in the study was assured.

Inclusion criteria: Any pregnant woman of any age with a singleton viable fetus near labour who consulted the Duhok Obstetrics and Gynecology teaching hospital and diagnosed to have preeclampsia and accept to participate in the study. The diagnosis of pre-eclampsia was made by NICE guideline criteria [(12)] which defined as new hypertension presenting after 20 weeks with one or more new-onset features, including significant proteinuria or maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological complications or hematological complications. The mild PE defined as gestational hypertension of at least 140/90 mmHg on two separate occasions ≥4 hours apart accompanied by significant proteinuria of >30 mgs/mmol, arising de novo after the 20th week of gestation in a

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previously normotensive woman and resolving completely by the 6th postpartum week according to the American College of Gynecologists and Obstetricians (ACOG) (3) and the International Society for the Study of Hypertension in Pregnancy (ISSHP) (13). While severe PE was defined as the presence of new onset of hypertension ≥ 160/110 mmHg occurs after 20 weeks' gestation (in a woman who had normal blood pressure before 20 weeks' gestation) or superimposed on pre-existing hypertension and one or more of the following:

1. proteinuria – spot urine protein:creatinine ratio ≥30 mg/mmol or ≥2+ on dipstick testing confirmed by a protein creatinine ratio test

2. other maternal organ dysfunction:

— renal insufficiency (creatinine >90 μmol/L, urine output of <80mL/4hr)

— liver involvement – elevated transaminases (ALT & AST) – at least twice upper limit of normal (right upper quadrant or epigastric abdominal pain). Note normal ranges are:

ALT 0-30 u/L and AST 10-50 u/L

— neurological complications (eg, eclampsia, altered mental status, blindness, stroke or, more

commonly, hyperreflexia when accompanied by clonus, severe headaches and persistent visual scotomata)

— haematological complications (thrombocytopenia – platelet count below 100 x 10^9/L, haemolysis)

3. uteroplacental dysfunction (fetal growth restriction).

Control group: Any pregnant normotensive woman ≥18 years old with a singleton viable fetus and accepted to participate in the research

The exclusion criteria were:
1- Chronic hypertension.

2- Diabetes mellitus type 1 and 2.

3- Cardiovascular disease.

5- Chronic renal disease.

6- Autoimmune disease.

7- Smoking.

8- Fetal anomalies.

9- Multiple gestations

10- Oligohydromniose and polyhydromniose.

11- Refused to participate.

Data collection Tool: The study collected data through a questionnaire assessing socio-demographic characteristics, obstetrics history, and antenatal care (ANC) services. Blood samples were taken from participants, and a full hematological and biochemical examination was performed. The D.Dimer level was estimated for all participants. Blood was collected via venipuncture and transported to the laboratory within 3 hours. If not possible, plasma was separated, frozen, and transported on dry ice. The

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concentration of plasma D.Dimer was measured using a manual D-Dimer kit, which was completed within 2 hours of the blood draw in the medical center laboratory.

Statistical analysis: The study used Microsoft Excel 2007 data and IBM-SPSS 26 for statistical analysis. Normality was tested using Shapiro-Wilk and parametric tests, and numerical variables were analyzed using Chi-square and Freeman-Halton exact tests. Differences among groups were compared using t-test and ANOVA, with a P-value of ≤ 0.05 considered significant.

Results:

Socio-demographic characteristics of the study sample were described in table (1). This table showed that the mean maternal age among the severe PE was (33.52±4.815 years) which was significantly higher (p=0.000) than that of control (25.32±6.569 years) and mild PE (27.64±6.650 years), no statistically significant difference was found between mild PE and control concerning the maternal age.

Regarding mean BMI, no statistically significant differences were found among the study groups. Furthermore, so significant differences were found among the study groups concerning the proportions of BMI classifications. Urban residence was frequent in control group 64.0%, while rural residence was frequent in mild and severe PE representing 66.0% and 82.0% respectively; the difference of type of residence among the study groups was statistically significant (p=0.000). Neither maternal educational levels nor occupations showed statistically significant differences among the study groups.

Table (1): Socio-demographic characteristics of the study sample.

Characteristics	**Control [n = 50]**	**Mild PE [n = 50]**	**Severe PE [n = 50]**	**P-value**
Mean maternal age (year)	25.32±6.569 **A**	27.64±6.650 **A**	33.52±4.815 **B**	**0.000**
Mean maternal BMI/ kg/m^2	27.30±4.744	27.72±4.076	27.30±4.744	0.867
Maternal BMI (kg/m$^{2)}$	**No. (%)**	**No. (%)**	**No. (%)**	**P-value**
Normal weight	17(34.0)	16(32.0)	6(12.0)	0.073
Overweight	6(12.0)	8(16.0)	12(24.0)	
Obese	27(54.0)	26(52.0)	32(64.0)	
Residence	**No. (%)**	**No. (%)**	**No. (%)**	**P-value**
Urban	32(64.0)	22(44.0)	9(18.0)	**0.000**
Rural	18(36.0)	28(66.0)	41(82.0)	
Maternal education	**No. (%)**	**No. (%)**	**No. (%)**	**P-value**
Illiterates	28(56.0)	29(58.0)	36(72.0)	0.509
Primary	8(16.0)	9(18.0)	7(14.0)	
Secondary	8(16.0)	5(10.0)	5(10.0)	
Higher	6(12.0)	7(14.0)	2(4.0)	

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Maternal job	No. (%)	No. (%)	No. (%)	P-value
Housewives	37(74.0)	41(82.0)	44(88.0)	0.197
Employees	13(26.0)	9(18.0)	6(12.0)	

BMI=Body Mass Index,PE: preeclampsia

Comparison of current obstetric history among the study sample was demonstrated in table (2) and revealed that the difference among the study group concerning the parity was statistically not significant (p=0.071). Antenatal care visits were found in 68.0% of control, 34.0% of mild, and 18.0% of severe PE groups; the difference was statistically significant (p=0.000).Moreover, statistically significant difference was found among those with adequate ANC visits (≥8 visits) of the three study groups in relation with those with inadequate visits (p=0.024). Previous history of PE was found in 34.0% of severe PE, 22.0% in mild PE, and 4.0% in of the control; the difference was statistically significant (p=0.001).

Table (2): Comparison of current obstetric history among the study sample.

Characteristics		Control [n = 50]	Mild PE [n = 50	Severe PE [n = 50]	P-value*
P0(primigravida)		28(56.0)	20(40.0)	30(60.0)	0.071
Multiparous (P1-4)		18(36.0)	24(48.0)	20(40.0)	
Grand multiparous (P≥5)		4(8.0)	6(12.0)	0(0.0)	
ANC		**No. (%)**	**No. (%)**	**No. (%)**	**P-value**
Yes		34(68.0)	17(34.0)	9(18.0)	**0.000****
No		16(30.2)	33(66.0)	41(82.0)	
If yes	**Adequate**	12(35.3)	12(70.6)	2(22.2)	**0.024*****
	Not	22(64.7)	5(29.4)	7(77.8)	
Previous history of PE		**No. (%)**	**No. (%)**	**No. (%)**	**P-value****
Yes		2(4.0)	11(22.0)	17(34.0)	**0.001**
No		48(96.0)	39(88.0)	33(66.0)	

*One-Way ANOVA test; ** Chi square test; ***Freeman-Halton Exact test; ANC=Antenatal Care, PE: preeclampsia

Comparison of the mean levels of D.Dimer among the study groups demonstrated in table (3) and revealed that the mean level showed escalated patterns from 1389.20±754.6 in the control group to 2097.7±229.59 in mild PE 5429.52±757.11 in severe PE. The difference between severe group and mild group and between severe group and control group were high enough to be statistically significant.

Table (3): Comparison of the mean levels of D.Dimer among the study groups.

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Investigations	Control [n = 50]	Mild PE [n = 50	Severe PE [n = 50]	P-value*
D.Dimer	1389.20±754.6 **A**	2097.7±229.59 **A**	5429.52±757.11 **B**	**0.000**

*One-Way ANOVA test; different letters means significance, and same letters means no significance; PE: precelampsia

Correlation between serum D.Dimer level and other parameters in the two study sample was demonstrated in table (4). This table revealed moderate inverse correlation between D.Dimer among the PE with Hb, platelets, and s. uric acid. Strong direct correlation was found with SGOT. Weak direct correlation was found between D. Dimer and each of S.creatinine and SGPT. Among the control group, the correlation of D.Dimer was weak and direct with S uric acid and weak inverse with SGPT.

Table (4): Correlation between serum D.Dimer level and other parameters in the two study sample.

Parameters	Correlation coefficient*	D. Dimer level	
		PE [n = 100]	Controls [n = 50]
Hb%	***r***	-0.614	-0.059
	P	**0.000**	0.684
Platelets	***r***	-0.785	-0.266
	P	**0.000**	0.062
Urea	***r***	0.158	0.084
	P	0.116	0.563
Creatinine	***r***	0.305	-0.086
	p	**0.002**	0.555
Uric acid	***r***	0.555	0.293
	p	**0.000**	**0.039**
TSB	***r***	0.137	0.029
	p	0.173	0.843
GOT	***r***	0.847	0.189
	p	**0.000**	0.189
GPT	***r***	0.394	-0.314
	p	**0.000**	**0.026**

= Correlation coefficient of the Pearson correlation; PE preeclampsia; Hb% hemoglobulin; TSB total serum bilirubin; GOT glutamic oxaloacetic transaminase; GPT glutamic pyruvic

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ransaminase

Area under the Curve for the cut-off points for serum D.Dimer level was demonstrated in table (5) and figure (1) and revealed that the D.Dimer had an excellent area under the curve (0.932) which was statistically significant (p=0.000).

Table (5): Area under the Curve for the cut-off points for serum D.Dimer level.

Area	Std. Error[a]	p-value.[b]	symptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.932	0.024	0.000	0.884	0.979

he test result variable(s): D. Dimer has at least one tie between the positive actual state oup and the negative actual state group. Statistics may be biased.

Under the nonparametric assumption

Null hypothesis: true area = 0.5

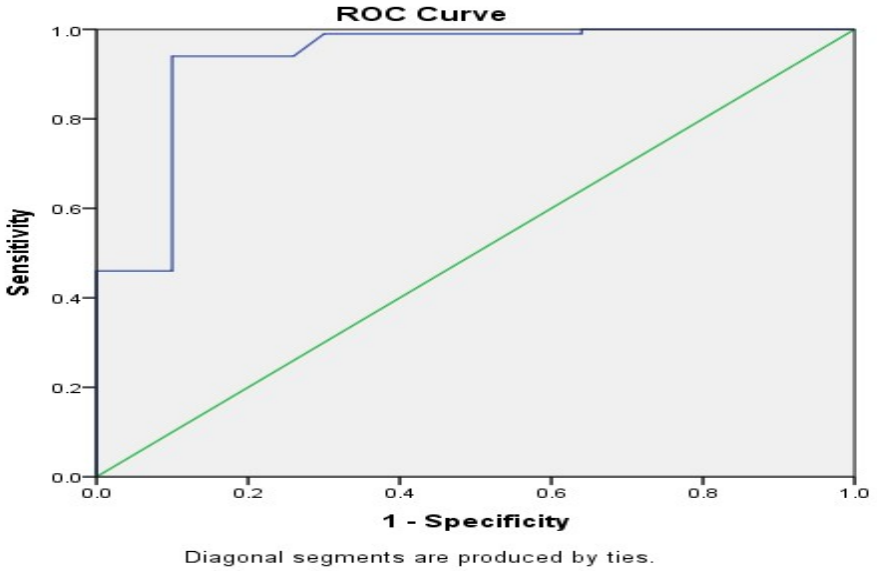

Figure (1): ROC curve test.

Cut-off points, sensitivity, specificity, positive predictive value, and negative predictive value for D.Dimer were demonstrated in table (6). This table showed that among these cut-off points, the 2500.0 point had the highest sensitivity and specificity to differentiate severe versus mild preeclampsia.

Table (6): Cut-off points, sensitivity, specificity, positive predictive value, and negative predictive value for D.Dimer

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Cut-points	SN%	SP%	PPV%	NPV%
1975.0	99.0	70.0	76.7	98.6
2047.5	94.0	74.0	78.3	92.5
2097.5	94.0	76.0	79.7	92.7
2125.0	94.0	78.0	81.0	92.6
2175.0	94.0	82.0	83.9	93.2
2225.0	94.0	86.0	87.0	93.5
2500.0	**94.0**	**90.0**	**90.4**	**93.8**
2775.0	92.0	90.0	90.2	91.8
2801.5	90.0	90.0	90.0	90.0
2826.5	88.0	90.0	89.8	88.2
2875.0	86.0	90.0	89.6	86.5

Discussion:

Preeclampsia, a hypertensive pregnancy disorder, accounts for 2% to 8% of pregnancy-related complications globally. Advanced maternal age has been linked to pre-eclampsia in various racial and ethnic groups, attracting the clinicians' attention [(2)].

The demographic and clinical characteristics of the studied groups were assessed and found that the maternal mean age among the severe group (33.52±4.815 years) was significantly higher than that among the mild eclampsia and controls. According to conclusively previous study [(14)], the increased age of women was an important risk factor for pre eclampsia due to increased villous reaction leading to pre eclampsia in a woman greater than 30 years, but the incidence of pre eclampsia in women less than 20 years of age is an area that has not been given much importance. In contrary, Kim *et al.,* [(15)] study reported that there were no statistical differences between the 2 groups in terms of maternal age.

Some studies have referred to obesity as a risk factor for preeclampsia and showed that the relationship between maternal weight and preeclampsia is a progressive risk and varies from 4.3% in women with a BMI < 19.8 Kg/m^2, up to 13.3% for women with a BMI ≥ 35 kg/m^2 [(16)]. The current findings showed no statistically significant difference among the studied groups. In a study by Vahid Roodsari *et al.,* [(17)] BMI was reported to be 24 kg/m^2 in the pre-pregnancy control group, 26.124 kg/m^2 in the gestational hypertension group, 26.24 kg/m^2 in the group with mild preeclampsia and 26.24 kg/m^2 in the severe preeclampsia group. In the research conducted by Andriani, Lipoeto, and Utama [(18)] that there is a relationship between BMI and preeclampsia incidence. However, overweight BMI is two times more risk for preeclampsia than women who have healthy body weight.

The present study demonstrated the significant association of the rural residence with severe and mild preeclampsia compared to urban predominance among the controls group. Previous study showed that adverse maternal outcomes among women with pre-pregnancy hypertension in rural communities may be further amplified by significant declines observed in access to obstetric services in recent years, with 45% of rural counties lacking obstetrics units [(19)].

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Maternal education in the current study showed to play no different role among the studied groups. Similarly, Ramesh *et al.,* [20] reported that there was no much difference in proportion of illiterate among both pre-eclamptic cases (22%) and controls (20%). Sole *et al.,* [21] study found that the high education reduced the risk for preeclampsia/eclampsia by 34% (adjusted odds ratio 0.66, 95% CI 0.62-0.69), compared with women with secondary education among nulliparous women, and by 39% (adjusted odds ratio 0.61, 95% CI 0.57-0.65) among parous women.

Housewives were frequently found among the study groups but statistically no significant difference was reported in the current study. This result run in parallel to that reported by Ramesh *et al.,* [20], in which no significant difference was found in occupation status between two groups. A study conducted by Nugteren *et al.,* [22] showed no difference between incidences of preeclampsia in non-working women compared to women with physical or stressful work.

Regarding the parity, the present study revealed that the difference among the studied groups was statistically not significant and highly associated with nulliparity. Likewise, the nulliparity is a risk factor for PE, and the incidence of PE is higher in primiparous than multiparous women as reported by Gold *et al.,* [23]. In contrary to the present study, Rangkuti *et al.,* [24] concluded that mothers with parity more than 3 tend to have pre-eclampsia with 23 cases (77%) while mothers with parity 1 are 7 cases (23%).

Antenatal care visits are early visits to midwives or physicians for pregnant women to receive antenatal care and prevent preeclampsia. A blood pressure check at the first visit aids health workers in early treatment. The government has implemented policies related to antenatal care programs. Based on the results of the current study, it was noticed that pregnant women who regularly visit antenatal and pregnancy care had lower potential to experience preeclampsia. Regular antenatal care is crucial for pregnant women to detect potential dangers early, allowing for easier prevention and treatment of preeclampsia, as it helps detect potential risks early on. In the same line, Saraswati study [25] found that pregnant women who are not routinely antenatal care are at risk of preeclampsia 17,111 times greater. Meanwhile, according to Nur [26] pregnant women who did not make antenatal visits risk 7,933 times affected by preeclampsia compared with mothers who visited antenatal> 2 times.

Previous history of PE among the controls of the present study was only 4.0% that increased in mild and severe PE up to 22.0% and 34.0% respectively, the difference was statistically significant. Historically, the first correlation identified as a risk factor for pre eclampsia has been a history of pre-eclampsia in the previous pregnancy. previous study have already established a relation between these two factors [27] but Ramesh *et al.,* [20] study showed an even stronger association between these two factors with an odds ratio of 58.5.

The mean concentrations of D.Dimer among the current studied groups were significantly differed; the level among the severe group was higher than that among mild and control and that among the mild was in turn higher than that among the controls. The median concentration of D-Dimer in maternal plasma was significantly higher in patients of severe pre-eclampsia than those of non-severe PE among those with PE. Considering substantial increase of D.Dimer concentrations throughout gestational age, this difference is more evident because the gestational age of the severe PE was significantly earlier than that of non-severe PE [28]. On seven studies comparing the rate of D.Dimer in PE and normal pregnancies, five studies found a slightly higher rate of D.Dimer than in controls, while the other two showed no difference. Pinheiro *et al.,* [29] and Baboolall *et al.,* [30] studied the role of D.Dimer levels in the prediction of the severity of PE. When D.Dimer dosage was performed at the time of PE, D.Dimer level was increased for patients with severe PE compared to mild PE. The dosage of D.Dimer appears to be more relevant when

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PE occurs, with a low predictive value. This result suggests that the D.Dimer level is a consequence of PMC and not of a modification preceding its occurrence. According to research by Manol *et al.,* [28], an elevated D.Dimer value in the third trimester of pregnancy is associated with the onset of preeclampsia. In contrary, Hovine *et al.,* [31] found that the serum D.Dimer level was not different in women with preeclampsia versus uncomplicated women.

The present study revealed moderate inverse correlation between D.Dimer among the PE with Hb, platelets, and s. uric acid. Strong direct correlation was found with SGOT. Weak direct correlation was found between D.Dimer and each of Serum creatinine and Serum GPT. Among the control group, the correlation of D.Dimer was weak and direct with S uric acid and weak inverse with SGPT. Zaitoun *et al.,* [32] study concluded that there was no significantly different between D.Dimer and hemoglobin levels among preeclamptic women when compared to normal pregnancy cases. Nigeria study [33] reported no significant correlation was found to exist between D.Dimer levels and platelet count. Although thrombocytopenia was not established in this study, there was evidence to show that pregnancy caused a significant reduction in the platelet count (194.1 ± 56.8 × 109/1) when compared with the non-pregnant control value of 231.6 ± 44.4 × 109/1. Also Jeremiah *et al.,* [34] reported a depressed platelet count during pregnancy of preeclamptic women. In the study conducted by Wang *et al.,* [35], blood urea and serum creatinine showed higher levels with increasing the titration of D.Dimer. A significant positive correlation between PE and ALP, LDH, and D.Dimer was reported by Duan *et al.,* [36].

By evaluation of the area under the curve for the cut-off points for serum D.Dimer level in the current study, an excellent (0.932) and statistically significant (p=0.000) area under the curve was found. In Zaitoun *et al.,* [32], the D.Dimer was highly sensitive and specific in diagnosis of sever preeclampsia (S.PET), D.Dimer >100 had 88% accuracy in prediction of sever preeclampsia. Also Kim *et al.,* [18], by using ROC curve analysis, a cut-off value of 1.19 mg/L (ROC area under the curve, 0.71; 95% confidence interval, 0.60 to 0.82; P=0.001) for maternal concentration of D.Dimer had 63.3% of sensitivity and 65.9% of specificity for the identification of severe preeclampsia.

Conclusions:

Pregnant women with PE tend to have a higher concentrations of D.Dimer. Area under the Curve for the cut-off points for serum D.Dimer revealed that the D.Dimer had an excellent area under the curve (0.932) which was statistically significant. The Cut-off point of 2500.0 point had the highest sensitivity and specificity to differentiate severe versus mild preeclampsia.

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