Inflammatory mediators (CA125, CRP) and uric acid in Association with severity of Preeclampsia in North Kordofan state, Western Sudan

Abstract

Introduction: Inflammatory mediators could be laboratory markers of preeclampsia, as the induction of an inflammatory process within the placenta may trigger the expression of Cancer antigen 125(CA125), C-reactive protein (CRP) and uric acid (UA). Regarding the pathophysiology of pre-eclampsia, there is defective trophoblastic invasion of uteroplacental blood vessels that leads to placental ischemia and induction of an inflammatory process within the placenta.

Objective: To evaluate the association of serum levels of cancer antigen (CA125), C-reactive protein (CRP) and serum uric acid with the Severity of Preeclampsia

Materials and Methods: the study recruited 200 singleton Sudanese pregnant women. These participants were <divided into three groups: control (n = 100) and cases (n = 100) which were further subdivided into; mild preeclampsia (n =46) and severe preeclampsia (n = 54).The three study groups were well-matched in maternal age, gestational age and body mass index. Blood samples were taken for measurement of serum cancer antigen-CA125, uric acid and C - reactive protein using immune- assay and enzymatic automated chemical analysis.

Results: The mean levels of cancer antigen-CA125 in mild and severe preeclampsia groups were 21.94±5.08(IU/ml) and 40.77±9.82 (IU/ml) respectively, which was significantly higher (P<0.001) in comparison with the control group (16.88±7.36 (IU/ml). There was a significant difference in the mean level of C-reactive protein in mild and severe preeclampsia 15.17±5.35 (mg/L), 31.49±12.56 (mg/L) compared with the control group (4.79±1.78 (mg/L), (P<0.01). Also, the mean levels of Uric Acid in mild and severe cases were 6.44±1.98 and7.37±2.00

which was significantly higher in comparison with the control (4.00±0.61); ($P<0.001$), there was also significant difference within the case (severe and mild) group ($P<0.05$).

CA125, CRP and UA level correlated positively with Mean Arterial blood pressure(MAP) where, ($r>0.7$; $P<0.001$). ROC curve validate the utility of these biomarker for the detection of preeclampsia severity (AUC>0.8; $P < 0.001$).

Conclusion: Serum cancer antigen 125(CA125), C- Reactive protein and Uric acid in studied preeclampsia groups were found to be significantly higher compared with the control group and the rises were directly associated with the severity of preeclampsia.

***Keywords*: Cancer antigen, C-Reactive protein, Uric Acid,Preeclampsia (PE), Sudan.**

Introduction:

Preeclampsia(PE) is a pregnancy-specific hypertensive disorder with multi- system involvement that originates in the placenta(1,2). PE remains the main cause of variable maternal and fetal morbidity and mortality in the developing countries(3). It complicates approximately 5 – 8 % of all pregnancies(4). It is characterized by the onset of hypertension (BP ≥140/90 mm Hg) and significant proteinuria (300 mg protein per day) occurring after the 20^{th} week of pregnancy in previously normotensive women(5). Many theories suggested its pathophysiology; including the failure of trophoblast invasion of uterine spiral arterioles, causing placental ischemia which triggers the expression of inflammatory factors in maternal circulation that may result in endothelial dysfunction which specifically gives the clinical picture of preeclampsia(6,7). It is associated with increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system(8–12).

The inflated maternal inflammatory response responsible for endothelial dysfunction may trigger expression of cancer antigen (CA125) and C-Reactive protein (CRP).

Cancer Antigen-125 (CA-125) is a high molecular weight glycoprotein complex antigen expressed by epithelial ovarian tumor(13,14). CA 125 is a marker of peritoneal and pleural disease(15) and was detected in the serum in many physiological and pathological conditions(16,17). Theextension of decidual destruction and separation of trophoblast from decidual areanticipated asthe primary means for the elevation of serum (CA-125) in

preeclampsia(18,19). It's role in obstetrics is not fully clarified as most clinical trials recommending its use are generally experimental in nature. There are few clinical studies related to the use of CA-125 in hypertensive disorders of pregnancy with conflicting results(20). However, some studies reported positive correlation between serum CA125 concentration and preeclampsia(21–24).

C - Reactive protein (CRP) is an acute phase protein produced by hepatocyte in response to release of Pro-inflammatory cytokines. It is a sensitive marker of systemic inflammation(22) responsible for the endothelial dysfunction in preeclampsia(25). Many studies reported its sensitivity and specificity in the prediction of PE(26–30).

Uric acid (UA) is a major end -product of purine catabolism(31) Hyperuricemia is the most consistent and earliest detectable changes in preeclampsia and was reported as a better predictor of foetal risk (32–35). Hyperuricemia has been related to cardiovascular and renal diseases through the generation of reactive oxygen species (ROS) and subsequent endothelial dysfunction(33,34,36–38). Another study revealed that the high level of serum uric acid was not steadily elevated in all women with severe preeclampsia suggesting that the uric acid was not a useful predictive test for PE(39).

According to the inconsistent results revealed by some previous works, we designed this study to measure the level of cancer antigen-125 (CA-125), (CRP) and (UA) and to determine their association with the severity of preeclampsia in Sudanese pregnant women.

Materialsand Methods:

The study was conducted at Elobeid teaching hospital, North Kordofan State, Western Sudan during period from December 2017 to December2020. Hundred patients with preeclampsia attending the antenatal ward and labour room, in the age range (15-50) years who fulfilled the criteria for pre-eclampsia were approached to participate in the study as cases. They were further divided into mild (46) and severe preeclampsia (54) according to the diastolic blood pressure (<110 or ≥110mmHg and systolic blood pressures<160 or ≥160mmHg) respectively(40). A number of 100 normotensive pregnant women, presenting to the same

outpatient clinics, were recruited as control group. Both groups were in the second half of pregnancy. Gestational age was calculated from the last menstrual period and confirmed by early first trimester ultrasound reports in suspected cases. Blood pressure was measured for all patients and controls with mercury sphygmomanometer. Patients having persistent high blood pressure ≥140/90 mmHg on 2 or more occasions 6 hours apart with proteinuria ≥ +2 by dipstick or ≥300 mg/day in 24 hours' urine collection were chosen for this study. Mean arterial blood pressure (MABP) for each subject was determined by the formula MABP [Diastolic blood pressure + (systolic blood pressure – diastolic blood pressure)/3].

Women with a history of ovarian, endometrial, or breast cancer or benign conditions such as endometriosis, multiple pregnancies, medical disorders such as diabetes mellitus, chronic hypertension, liver, renal, and cardiovascular disease or inflammatory conditions were excluded from the study. Structured questionnaire was used to gather socio-demographic characteristics and a written informed consent was obtained from all participants. The ethical clearance was obtained from Ministry of Health, North Kordofan State- Sudan and Research Board at the Faculty of Medicine, University of Kordofan.

Sample Collection:

Five ml of venous blood was collected from both groups by venipuncture in plain tubes. Samples were kept at room temperature for 30 minutes to clot then centrifuged at 2000 rpm for 10 minutes and serum was stored at -20 C° until the assay.

Inflammatory mediators Measurement:

The serum level of cancer antigen-125 (CA-125), was measured for both patient and control groups by automated chemical analyzer (Mindary CL-1200iChemiluminescene Immunoassay System-India) using antigen –antibody reaction**.** Serum (CRP) and UA levels were measured by (Mindary Bs200 Automated Benchtop Chemistry Analyzer-India) using enzymatic reaction according to the manufacturer's instructions.

Statistics Analysis:

Data was entered, coded and analyzed using statistical package for social sciences version 20 software (SPSS Software, Chicago Inc., USA). Data was expressed as mean ± SD. The t-test

was used to compare the two groups (cases and controls). While One-way ANOVA was used to compare the parametric variables of the three groups (control, mild, and severe preeclampsia). *P* value of <0.05 was considered significant. Pearson correlation was done to find correlation coefficient value (r) either positive (direct correlation) or negative (in verse correlation) with value < 0.3 represents no correlation, 0.3 - <0.5 represents weak correlation, 0.5 - < 0.7 represents moderate correlation and > 0.7represents strong correlation. Multiple Receiver Operating Characteristic curve (ROC) was drawn to evaluate validity of CA125, CRP and UA in predicting pregnant women at risk of preeclampsia disease and its severity. The test was considering good marker if it shows area under the curve (AUC ≥0.8).

Result:

A total of 200 pregnant women: (100) cases of PE and (100) controls were recruited during the study period. Socio-demographic and obstetric data of the studied women are described in Table1. Both groups were matched in age, body mass index and gestational age among PE patients with respect to the normotensive pregnant women.

Table1: Clinical and Demographic Characteristic of the Patients groups (mild and severe preeclampsia) and control group.

VARIABLES	CONTROL (n=100) Mean ±SD	MILD PE (n=46) Mean ±SD	SEVERE PE (n=54) Mean ±SD	*P*-Value
Age(years)	26.67± 6.74	26.68± 6.31	26.33±7.47	0.987
BMI	26.78± 4.02	27.56± 4.97	27.93± 4.49	0.145
Gestational age (weeks)	33.67± 4.59	33.82± 3.81	34.46± 4.96	0.641

There is no significant difference (*P*>0.*05*) in the maternal age, BMI and gestational age.

Regarding, the mean levels of CA-125, CRP and UA, they were statistically significantly higher in severe and mild PE group in comparison with the control group(p<0.001) The mean level of UA also significantly different in severe and mild PE group in comparison with the control group(p<0.05) as shown in table2.

Table 2: (Mean ±SD) of Serum Cancer Antigen(CA125), CRP, UA and MAP in the patient's group and control groups.

VARIABLES	CONTROL (n=100) Mean ±SD	MILD PE (n=46) Mean ±SD	SEVERE PE (n=54) Mean ±SD	P- VALUE
CA125	16.48± 5.84	21.94± 5.08	40.78± 9.82	< 0.001
CRP	4.79±1.78	15.17±5.35	31.50±12.56	< 0.001
UA	4.00±0.61	6.44±1.98	7.37±2.00	< 0.05
MAP	84.15±9.6	115.89±5.95	136.06±8.92	< 0.001

Table 3:**The coefficient correlation(r) of CA-125, CRP and UA with MAP in preeclampsia.**

parameters	coefficient correlation(r)	*P*-value
CA125	0.771	0.001
CRP	0.808	
UA	711	

Our study revealed a strong positive correlation between CA-125, CRP and UA levels and Mean Arterial blood;(r> 0.7, P < 0.001).

According, to the Pearson coefficient correlation test, MAP was found to have a significant effect on the increase in CA125, CRP and UA in preeclampsia as shown in figure1,2 and 3 respectively.

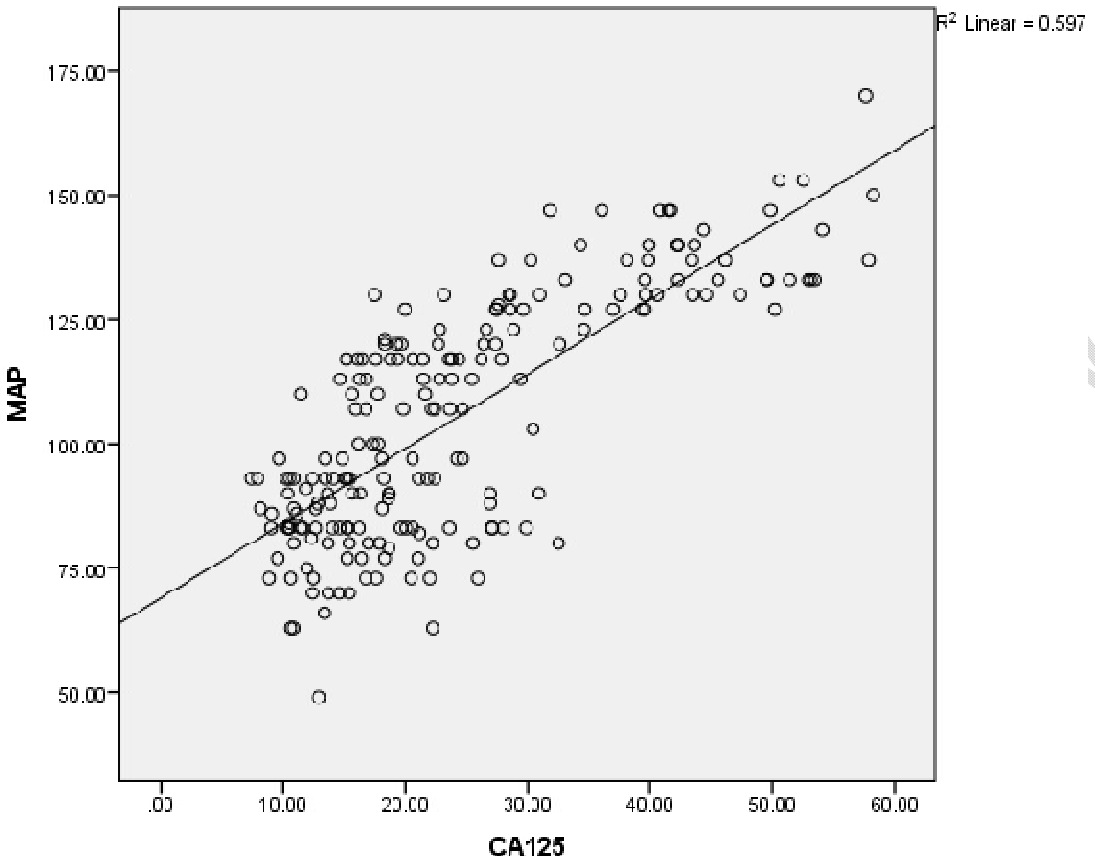

Figure 1: Significant correlation of CA125 and MAP in the study groups (mild and severe preeclampsia). MAP = 40 + 2.333 CA125 (regression equation according to coefficients table) ($t = 17.11$, $p < 0.001$).

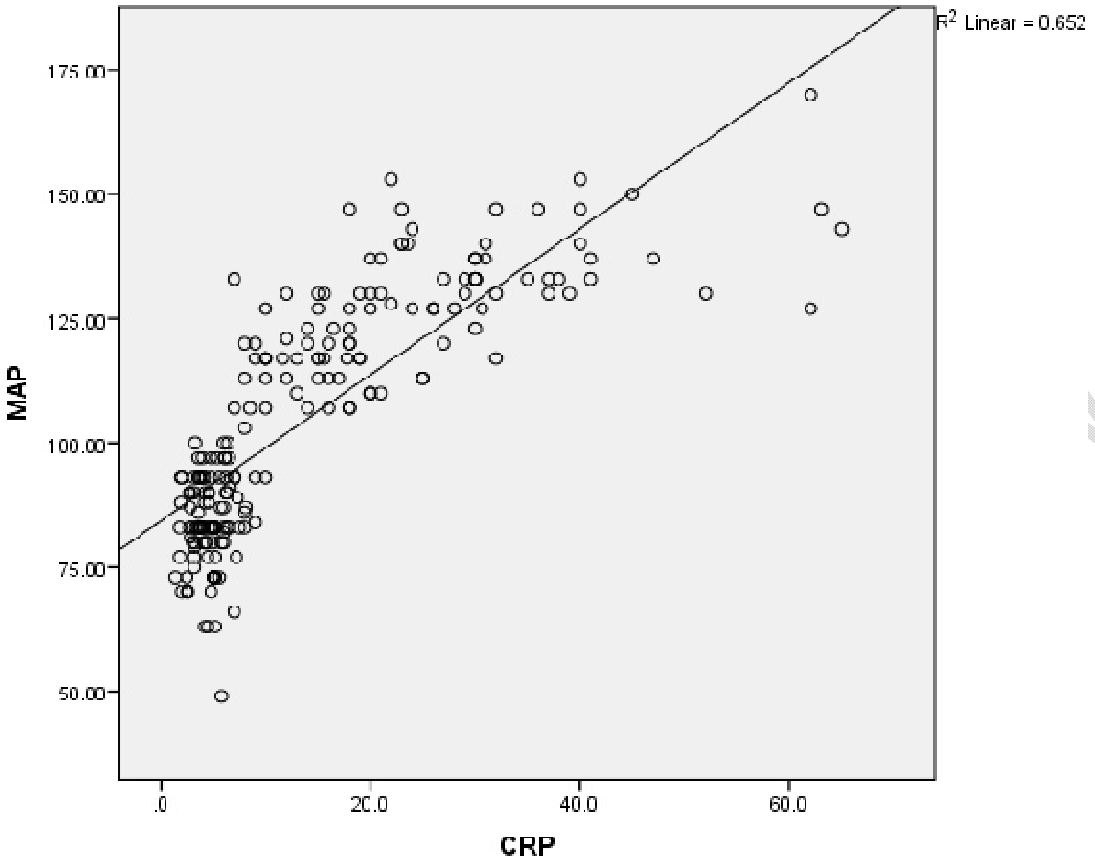

Figure 2: Significant correlation of CRP and MAP in the study groups (mild and severe preeclampsia). MAP = 40 + 2 CRP (regression equation according to coefficients table) ($t = 19.27$, $p < 0.001$).

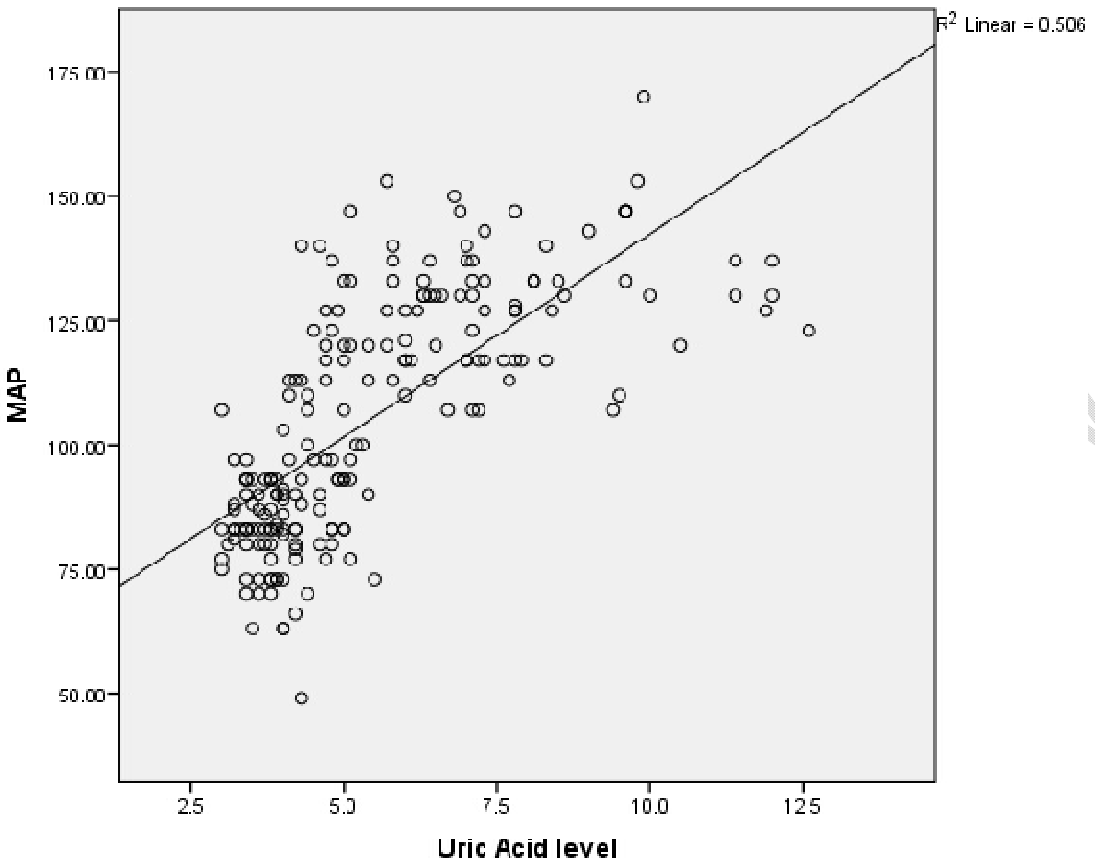

Figure 3: Significant correlation of UA and MAP in the study groups (mild and severe preeclampsia). MAP = 16.6667+11.6667 UA (regression equation according to coefficients table) ($t = 14.24$, $p < 0.001$).

Multiple Receiver Operating Characteristic curve was drawn to evaluate validity of CA125, CRP and UA in predicting pregnant women at risk of preeclampsia disease and its severity. As shown in figure 4

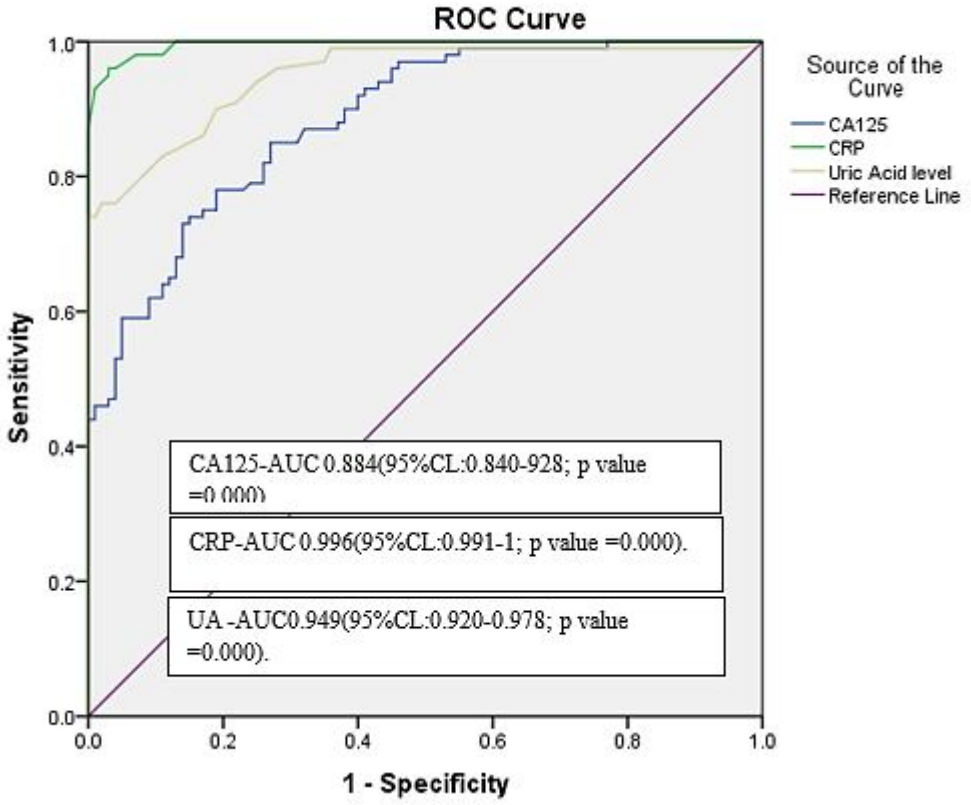

Figure 4:ROC curve of serum CA125, CRP and UA levels in preeclampsia.

The sensitivity of CA125 was (85%), the specificity was (73%), while the sensitivity of C – reactive protein was (95%), the specificity was (97%), and sensitivity of Uric acid was (86%), the specificity was (83%).

Discussion:

Pre-eclampsia is a multisystem disorder of unknown etiology that constitutes a major cause of maternal and foetal morbidity and mortality worldwide(41)(42),

In the present study, Demographic data of the patient and control groups showed no significant differences with respect to maternal age, gestational age and BMI. confirming the demographic equivalence in the two groups (patient and control).

In the current study preeclampsia was found to be associated with an increased level of CA125, CRP and UA among patients in comparison with controls group. The CA-125 levels were significantly higher in severe and mild PE incomparison with the control group ($p<0.001$); CA-125 levels were higher in severe preeclampsia when compared to mild preeclampsia($p<0.001$). Our study revealed a strong positive correlation between CA-125 levels and Mean Arterial blood pressure(MAP) in preeclampsia ($r> 0.7$, $P < 0.001$) as demonstrated in figures(1) which is consistent with previous studies stated by other authors(28,43).

Receiver operating characteristic (ROC) curve of serum CA125 in preeclampsia indicating the validity of CA125 as a sensitive and specific prognostic tool for the prediction of PE severity; (AUC>0.8; P<0.001) as shown in figure 4. The elevation of CA-125 in PE patients in this study agree with many previous studies(21,23,28,44) in which some authors suggesting that CA125 is a promising biochemical marker and can reflect the severity ofpreeclampsia (7,11,18,21,23,28,43,45–47),this finding might be due to failure in trophoblastic invasion and the induction of an inflammatory process within placenta that triggers the expression of CA-125and anticipated to be anessential mechanism for elevation of serum CA125 in preeclampsia. In contrast to our result Schro¨cksnadel et al. and Bon et.al found no statistically significance difference in CA- 125 between patients and control groups(16,20). This inconsistence finding with our result might be due to different sample size, demographic and genetic variations and different timing of CA125 measurementduring pregnancy.

Moreover, our study showedan elevation in the mean level of CRP in mild and severe PEpatients in comparison with the control group($p<0.001$) and these escalations directly correlated with the severity of preeclampsia($p<0.001$). This finding is in agreement with that obtained previously by many authors(24,27–30,47) where Serum CRP was significantly positive correlated with MAP($r>0.7$, $p<0.001$). As systemic inflammatory response is one of pathophysiological mechanisms of PE, CRP was more sensitive and specific to predict PE in pregnant women (AUC= 0.9) Figure 4. The increment in CRP was directly correlated with the severity of the disease; hence it can be used for early prediction of severity of PE.

However,contrasting studies (26,48)found no association between the maternal inflammatory mediator CRP and established PE.

Furthermore, the study indicated significantly higher difference in the mean values of UA level in the patients group (mild and severe) in comparison with the control group(p<0.001) and significant different between severe and mild (P>0.05).UA showed strong positive correlation with MAP (r>0.7, P<0.001) and (AUC= 0.94) as illustrated in Figure 4. This elevated- serum uric acid levels consistent with other reported results (34,49,50). Soluble uric acid impairs the vasodilating-nitric oxide generation in endothelial cells inducing endothelial dysfunction and pre-eclampsia(37). Recent evidence(51) supports a role for uric acid as a true cardiovascular risk factor, particularly for the development of hypertension and renal disease(49,52). The rise in uric acid levels in preeclampsia is due to placental injury, which causes purine catabolism and uric acid generation. However, our finding is contradicted with otherswho reported that high level of serum uric acid was not consistently found elevated in all women with severe preeclampsia, suggesting that the uric acid could not be a useful prognostic test as stated byAmat-Al Karem(39). However, Kanti Mandal *et al.*, 2015 stated that serum UA and CRP may be possible to use as biomarkers for identifying women at risk of Preeclampsia(53).

This study also revealed a strong positive correlation between CA-125, CRP and UA levels and Mean Arterial blood pressure(MAP) in preeclampsia (r> 0.7, P < 0.001) as demonstrated in (figures1,2 and3) which is consistent with previous studies stated by other authors(43)(28).

According to the results of specificity and sensitivity of CRP and CA 125, levels obtained in the current study, emphasizes the potential role these markers as predictive test for severity of PE.

Additionally, our study indicates that CA-125 can be used as a marker in preeclampsia follow-up. Since it is much more available and comparatively less expensive, it seems to be a promising test for screening preeclampsia.

Conclusion:

There wereincreased levels of CA-125, CRP and UA levels in women with preeclampsia which were correlated with the severity of the disease. This study suggested that CRP and CA-125 are biochemical markers which reflects the severity of the inflammatory process in

preeclampsia. Similarly, UA may be a useful biomarker for identifying women at risk of preeclampsia.

Limitations:

Our study is hospital-based limited by the availability of patients; therefore, a convenient sample size might be under representative to the general population., researches with large sample size and at different gestational ages are needed to clear up the association of elevated serum CA-125 level in Sudanese women with severe preeclampsia.

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