

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 two groups: control (n = 100) and cases (n = 100). The cases were further subdivided into; mild preeclampsia (n =46), and severe preeclampsia (n = 54). The 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 were significantly higher, ($P<0.001$) in comparison with the control group (16.88±7.36 (IU/ml). The mean levels of C-reactive protein in mild and severe preeclampsia were; 15.17±5.35 (mg/L), 31.49±12.56 (mg/L) respectively. There was significant difference in their levels, compared to 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 and 7.37±2.00 which was significantly higher, in comparison with the

control (4.00 ± 0.61); ($P < 0.001$). The level of uric acid also, showed significant difference within the case (severe and mild) group ($P < 0.05$). CA125, CRP and UA levels correlated positively with Mean Arterial blood pressure (MAP), ($r > 0.7$; $P < 0.001$). 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 ($BP \geq 140/90$ mm Hg) and significant proteinuria (300 mg protein per day), occurring after the 20th 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 and 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). “The extension of decidual destruction and separation of trophoblast from decidua, are anticipated as the 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 fetal 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 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.

Materials and Methods:

The study was conducted at Elobeid teaching hospital, North Kordofan State, Western Sudan during period from December 2017 to December 2020. Hundred patients with preeclampsia attending the antenatal ward and delivery 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 \geq 110mmHg, and systolic blood pressures <160 or \geq 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 $\geq 140/90$ mmHg on 2 or more occasions 6 hours apart, with proteinuria $\geq +2$ 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 $MABP = \text{Diastolic blood pressure} + \frac{\text{systolic blood pressure} - \text{diastolic blood pressure}}{3}$.

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.

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, and were then centrifuged at 2000 rpm for 10 minutes, and serum was stored at $-20\text{ }^{\circ}\text{C}$ 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-1200i Chemiluminescence 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 \pm 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 > 0.7 represents 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 showed area under the curve ($AUC \geq 0.8$).

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 Patient's groups (mild and severe preeclampsia) and control group.

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

There was no significant difference ($P > 0.05$) in the maternal age, BMI, and gestational age.

Table 2: (Mean \pm SD) of Serum cancer antigen(CA125), CRP, UA and MAP in the patient's group and control groups.

VARIABLES	CONTROL (n=100)	MILD PE (n=46)	SEVERE PE (n=54)	P- VALUE

	Mean ±SD	Mean ±SD	Mean ±SD	
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

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, was significantly different in severe and mild PE group in comparison with the control group ($p < 0.05$) as shown in table 2.

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	0.711	

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 figure 1, 2 and 3 respectively.

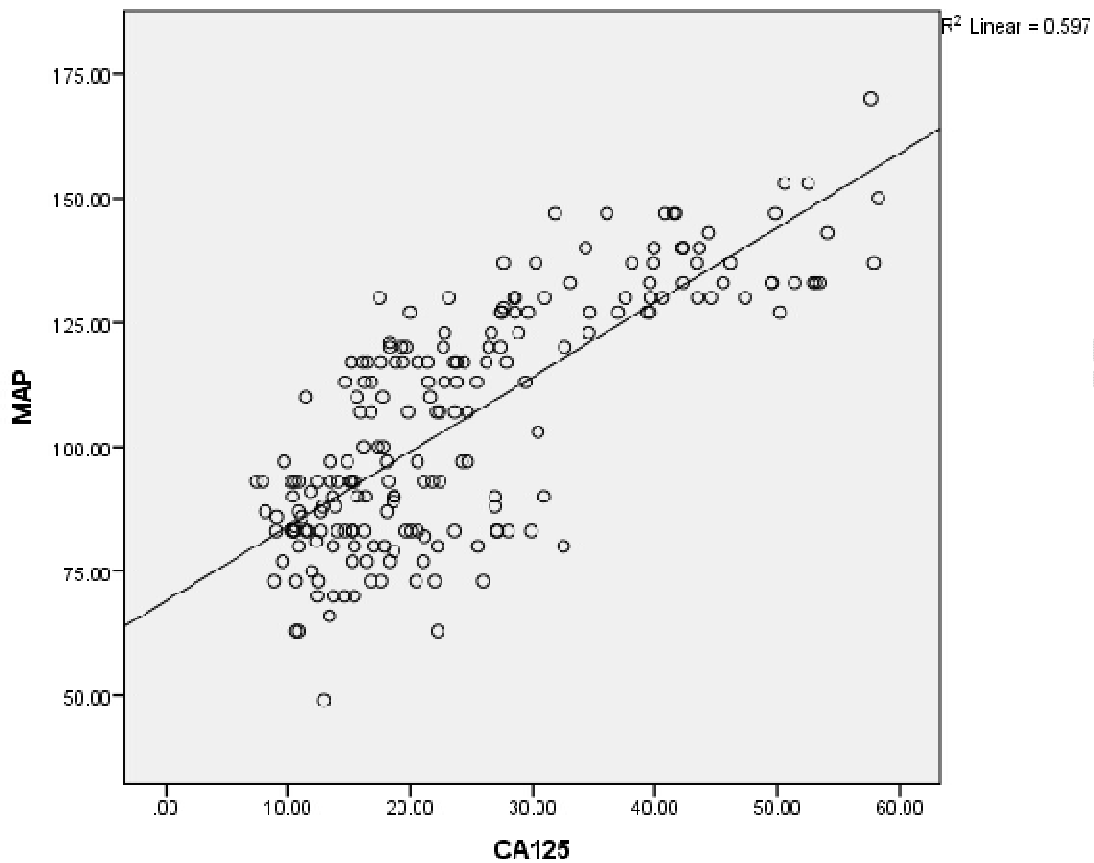


Figure 1: Significant correlation of CA125 and MAP in the study groups (mild and severe preeclampsia). $MAP = 40 + 2.333 \text{ CA125}$ (regression equation according to coefficients table) ($t = 17.11, p < 0.001$).

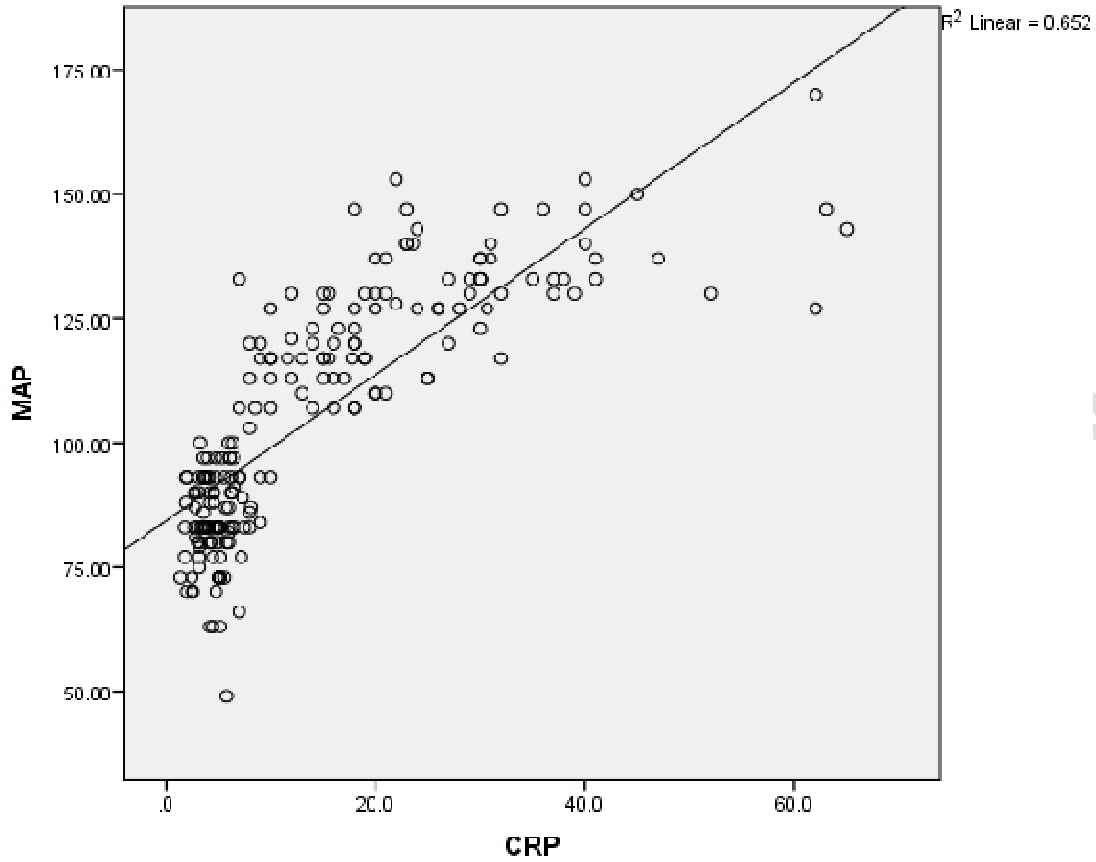


Figure 2: Significant correlation of CRP and MAP in the study groups (mild and severe preeclampsia). $MAP = 40 + 2 \text{ CRP}$ (regression equation according to coefficients table) ($t = 19.27, p < 0.001$).

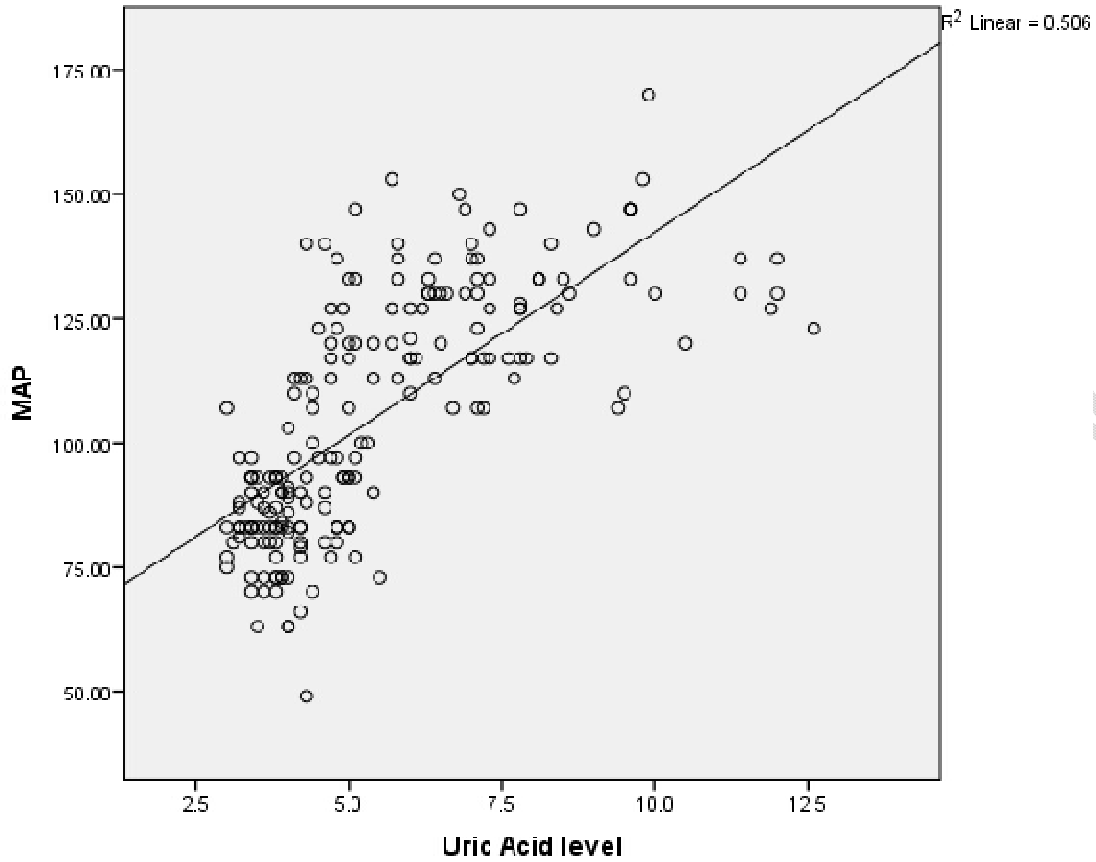


Figure 3: Significant correlation of UA and MAP in the study groups (mild and severe preeclampsia). $MAP = 16.6667 + 11.6667 \text{ UA}$ (regression equation according to coefficients table) ($t = 14.24$, $p < 0.001$).

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

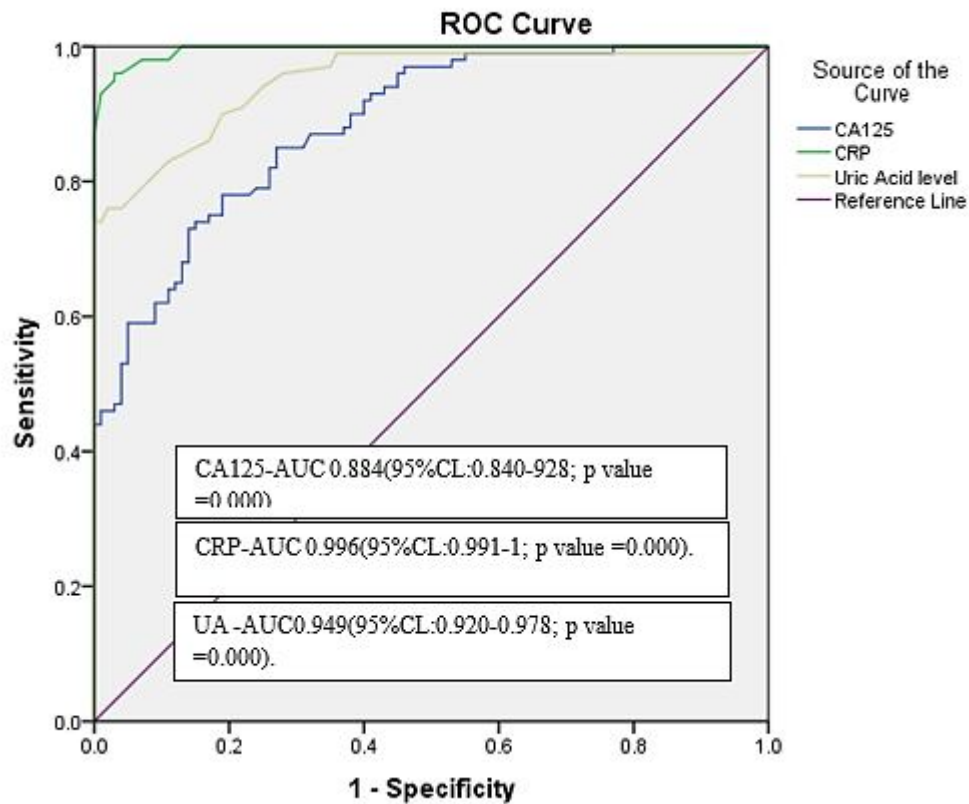


Figure 4:ROC curve of serum CA125, CRP and UA levels in preeclampsia.

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 fetal 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 in comparison with the control group ($p < 0.001$); CA-125 levels were higher in severe preeclampsia when compared to mild preeclampsia ($p < 0.001$), and this suggests the association of its level with preeclampsia severity. 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 agreed 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 of preeclampsia (7,11,18,21,23,28,43,45–47). “This rising level of CA-125, might be due to failure of trophoblastic invasion, and the induction of an inflammatory process within placenta, that triggers the expression of CA-125. In contrast to our result Schrocksadel et al. and Bon et al found no statistically significant difference in CA- 125 between patients and control groups”(16,20). This inconsistency finding with our result might be due to different sample size, demographic and genetic variations, and different timing of CA125 measurement during pregnancy. In addition, the variable degrees of failure of trophoblast invasion, might be a causative factor of such variation in biochemical markers levels.

Moreover, our study showed an elevation in the mean level of CRP in mild and severe PE patients 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 positively 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 patient's 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 was 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 level in preeclampsia is due to placental injury, which causes purine catabolism and uric acid generation. However, our finding is contradicted with others who 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 by Amat-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 (figures 1, 2 and 3) which was 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:

Our study demonstrated increased 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 reflect 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.

Ethical Approval and consent

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.

Conflicts of interest: no conflicts of interest among authors

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