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Estimation of serum uric acid level in 1st and early 2nd trimester (<20 WKS) as a predictor of preeclampsia and perinatal outcome

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Abstract
Background:
1. Hypertension is one of the common medical complications of pregnancy and contributes significantly to maternal and perinatal morbidity.
2. The identification of Pre-eclampsia and effective management play a significant role in the outcome of pregnancy, both for mother and baby.
3. In developing countries like India, with inadequately cared pregnancy, this entity remains undetected till major complications supervene.
4. Henceforth this is a study attempt to predict the development of pre-eclampsia from maternal serum uric acid levels in 1st and early 2nd trimester(<20 wks) and assess the perinatal outcome.

Objectives: To predict preeclampsia and to assess perinatal outcomes from serum uric acid level testing in 1st and early 2nd trimester (<20 wks).
Method: All pregnant women in their 1st and early 2nd trimester(up to 20 Wks gestation) visiting OPD and also in-patients at MVJMC&RH are explained about the study, with informed consent, their serum uric acid levels are measured. These women are followed up in their antenatal visits and also during peripartal period for development of any features of pre-eclampsia and also the perinatal outcome assessed in terms of IUGR, NICU admission, low APGAR scores, low birth weight and other complications. The patients who developed preeclampsia are grouped as preeclampsia Cohort. The patients who are normotensive till delivery are grouped as normal cohort. The factors taken for analysis are age, obstetric score, serum uric acid APGAR score, birth weight, NICU admission.
Results: A total of 100 cases of pregnant women in 1st and early 2nd trimester (upto 20 wks) were included in this study with maximum number of patients in the age group of 26-30years (42%) and most were primigravida (45%).Out of 21 patients who developed preeclampsia,15(71.4%) had positive serum uric acid test, out of 6 women who delivered IUGR babies,4(66.7%) had positive uric acid test.Among 100 women, 30 women delivered babies required NICU care. among these 30, 21(70%) had positive maternal uric acid test antenatally, out of 39 who had APGAR score at 1min <7, 28(71.8%) babies had positive maternal serum uric acid test and out of 36 who had APGAR score at 5min <7, 22(61.1%) babies had positive maternal serum uric acid test. Out of 28 low birth weight babies (<2.5kg), 22(78.6%) had positive maternal serum uric acid test.
Interpretation and Conclusion: In present study increased serum uric acid level in first trimester and early 2nd trimester(<20 wks) is associated with development of preeclampsia in later weeks of pregnancy and also raised level of serum uric acid level in first trimester and early 2nd trimester(<20 wks) helps to determine fetal and maternal outcome and is associated with increased risk of preeclampsia, low birth weights(<2.5 kg), low APGAR scores and increased NICU admissions.

Keywords: Intrauterine growth restriction, APGAR score, Neonatal Intensive Care Unit

Introduction
Hypertensive disorders of pregnancy (HDP) are among the most common medical disorders during pregnancy and are considered to be a major cause of maternal and fetal morbidity and mortality. In developing countries, HDP ranks second only to anemia with approximately 7-10% of all pregnancies complicated by some form of hypertensive disorder and lead to various maternal and fetal complications [1]. In India, the incidence of pre-eclampsia, as recorded from hospital statistics, varies widely from 5-15%, while that of eclampsia is about 1.5% [2]. Strangely, the exact etiopathogenes is for HDP, including pre-eclampsia and eclampsia, still

remains obscured and presents an interesting unsolved mystery in obstetric practice.

Uric acid, which is one of the end product of purine metabolism is elevated in patients of preeclampsia because of decreased renal clearance and increased production [3]. Decreased renal clearance is due to altered renal tubular function and overproduction of uric acid due to increased breakdowns of purines in placenta. This uric acid impairs nitric oxide production which results in endothelial cell dysfunction which plays a role in pathophysiology of Preeclampsia.

Estimation of serum Uric Acid level is a simple biochemical test, which quantitates the extent of cellular death and thereby the assessment of severity of preeclampsia.

In the present study, we attempt to look into the maternal serum uric acid (UA) levels as a predictor of preeclampsia and its association to fetal outcome. It has been observed in various studies in the past that the serum uric acid can predict severity of disease [4] while some studies and reviews have not been able to confirm this.

Review of literature

A prospective clinical observational study by Nair *et al*. [5] conducted in 2017,Vydehi institute of medical sciences and research institute, Bangalore, 50 pregnant women with severe pre-eclampsia and 50 normotensive women were included and maternal serum uric acid level was estimated in both groups to evaluate severity of pre-eclampsia with raised uric acid level and perinatal outcome. The study concluded that there was a positive correlation between serum uric acid level and severity of pre-eclampsia and adverse fetal outcome was observed with raised maternal serum uric acid level in preeclamptic patients.

A Study was done by Disha *et al*. [6] conducted at the Civil Hospital, Ahmedabad in 2012, where 80 Hypertensive women were selected randomly and retrospectively studied. Birth weight, Gestational age at delivery, complications like HELLP, eclampsia, IUD, abnormality in platelet count, creatinine, bilirubin were noted. Groups were divided into 2 based on uric acid levels as <6 mg/dL and >6 mg/dL and all variables correlated. In this study, increase in fetal and maternal complications were noted in group with uric acid >6mg/dL (p <0.05). Mean gestational age at delivery and mean birth weight were reduced in group with uric acid >6 mg/dl.

A prospective study by Sreelatha *et al*. [7], ESI Post-Graduate Institute of Medical Science and Research, Bangalore from Jan to Aug 2014, in which 80 pregnant women with mild and severe GHT were included Uric acid and LDH were estimated. The women were followed up till delivery and early post-partum. Gestational age at delivery, birth weight, mode of delivery, fetal and maternal complications were noted. Significant association was found between LDH and uric acid with severity of pre-eclampsia, maternal morbidity, birth weight of babies. Neonatal outcome was not statistically significant in this study.

A prospective study by Patel *et al*. [8] conducted in the department of obstetrics and gynecology, BJ medical college and hospital, Ahmedabad, Gujarat, in 2014 on two groups of 50 women each with HDP. The first group comprising of 50 patients with serum uric acid level of ≥6 mg/dL was compared to the second group of 50 patients with serum uric acid level of <6 mg/dL. Maternal complications like eclampsia, HELLP syndrome, ARF and fetal complications like IUD, low Apgar score, and IUGR were studied. The study revealed that hyperuricemia in patients with HDP was a strong risk factor for several maternal complications with an increased risk fetal complications like Apgar score of <7 by 6-fold, IUFD by 20-fold, IUGR by 4-fold, eclampsia by 4.2-fold, and C-section by 3.4-fold in the group with serum uric acid level of ≥6 mg/dL.

According to the National High Blood Pressure Education Program (NHBPEP) [9] and American College of Obstetricians and Gynecologists(ACOG) [10], hypertension is defined as:

1. Systolic BP of ≥140 mmHg and/or
2. Diastolic BP of ≥90 mmHg (Korotkoff V) that is measured on 2 occasions, 4-6 hrs apart, within a 7-day period.

Increase in systolic blood pressure by 30 mmHg or by 15 mmHg diastolic pressure above the patient's baseline was abandoned as the diagnostic criteria in hypertension as it could not prove to be a good prognostic indicator. Pre-eclampsia is a multi-organ disease of unknown etiology that leads to the development of hypertension and proteinuria at or after 20 weeks of gestation. Classically defined as the triad of hypertension, edema and proteinuria, recent definitions exclude edema due to lack of specificity. Presence of proteinuria remains an important diagnostic criterion in differentiating pre-eclampsia from gestational hypertension**.**

Risk factors for pre-eclampsia [11]

There are certain risk factors which make certain individuals/pregnancies more prone to developing GHT and complications thereof, such as pre-eclampsia. These risk factors can be couple related, maternal or pregnancy related, or due to pre-existing medical conditions. The table shows the risk factors.

Table 1: Show the couple related

Couple Related	Maternal or Pregnancy Related	Pre-Existing Medical Conditions
First paternity Limited sperm exposure Pregnancy after donor insemination, donor egg, donor embryo	Extremes of age (teenage and >35 years) Parity Interval from last pregnancy>10 years Insulin resistance/ Gestational diabetes	Obesity Pre-gestational diabetes Chronic hypertension Renal disease Maternal immunologic disease Thrombophilia
	Smoking Multifetal pregnancy Hydrops fetalis Hydatiform mole Pre-eclampsia in previous pregnancy Family history of pre- eclampsia Maternal low birth weight Abnormal uterine artery Doppler at 18- 24 weeks	Antiphospholipid antibody syndrome

Complications of pre-eclampsia: The complications are studied under two heads: Maternal and Fetal complications.

Table 2: The complications are studied under two heads: Maternal and Fetal complications

Maternal Complications	Fetal Complications
Abruptio Placentae (most common) HELLP Syndrome Pulmonary edema Thrombocytopenia/Disseminated Intravascular Coagulation Acute renal failure Adult respiratory distress syndrome Eclampsia Hepatic rupture Cerebral hemorrhage Sudden post-partum collapse	Intra-uterine growth retardation (IUGR) Pre-maturity Ante-partum and Intra-partum asphyxia Intra-uterine death (IUD)

Table 3: Predictive tests for the development of pre-eclampsia

Modality Tested	Tests
Placental Perfusion/Vascular Resistance	Roll-Over Test [12], Isometric Handgrip Test, Pressor Response to Angiotensin-II Infusion [12], Mid- trimester Mean Arterial Blood Pressure [13], 24-Hr
	Ambulatory Blood Pressure Monitoring, Uterine Artery Doppler Velocimetry, Pulse Wave Analysis [13]
Fetoplacental Unit Endocrine dysfunction	α-Fetoprotein, Human Chorionic Gonadotrophin (Error! Bookmark not defined.), Estriol, Pregnancy- Associated Plasma Protein-A, Inhibin-A, Activin-A, Placental Protein-13, Corticotropin-Releasing Hormone
Renal Dysfunction	Serum Uric Acid [14], Microalbuminuria, Urinary Calcium (Error! Bookmark not defined.), Microtransferrinuria, Cystatin-C
Endothelial Dysfunction/Oxidative Stress	Platelet Count, Platelet Activation, Lactate Dehydrogenase, Fibronectin [15], Prostaglandins, Prostacyclins, Thromboxane, C-Reactive Protein, Cytokines, Endothelins, Homocysteine, Anti- Phospholipid Antibody, Placental Growth Factor (PIGF), Vascular Endothelial Growth Factor (VEGF), sFlt-1
Others	Antithrombin-III, Atrial Natriuretic Peptide, β2- Microglobulin, Haptoglobin, Cell Free Fetal DNA, Serum and Urine Proteomics, Hepatic Aminotransferases

URIC ACID

Uric acid is the end-product of purine metabolism. Its level is elevated in pre-eclampsia due to its decreased renal clearance or by its increased production by breakdown of purines in placenta. Decreased renal clearance is due to altered renal tubular function. This uric acid impairs the generation of nitric oxide from endothelial cells causing endothelial cell dysfunction which is the main pathophysiology in pre-eclampsia. Hence it is used as the predictive marker for pre-eclampsia. Various studies have been done on uric acid levels in pre-eclamptic patients and correlation with severity of disease, maternal and fetal complications.

Role of uric acid in preeclampsia [16].

1. One of the earliest Bio chemical lab manifestations in Preeclampsia
2. It is results from reduced uric acid clearance from diminished GFR, increased tubular reabsorption and decreased secretion [17]

Normal uric acid levels

Table 4: References from Williams text book of Obstetrics 24th edition.

URIC ACID (MG/DL)	Non pregnant adult	1st trimester	2nd trimester	3rd trimester
	2.5-5.6	2.0-4.2	2.4-4.9	3.1-6.3

Results

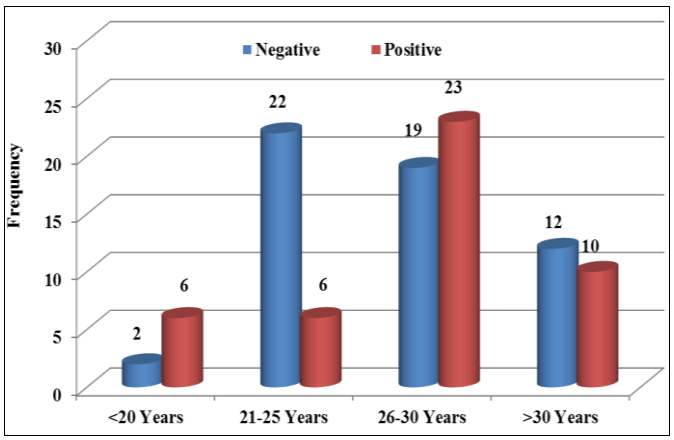

Fig 1: Age distribution

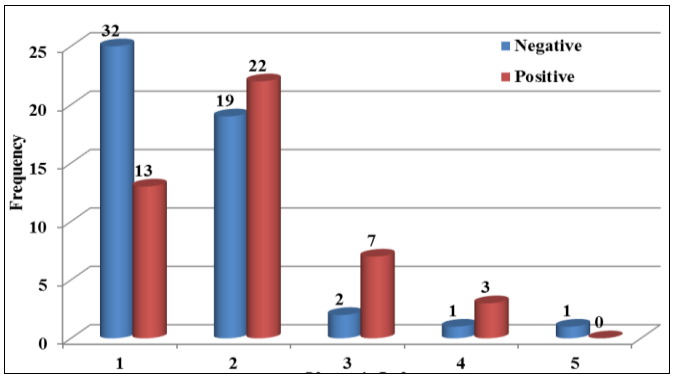

Fig 2: Obstetric index

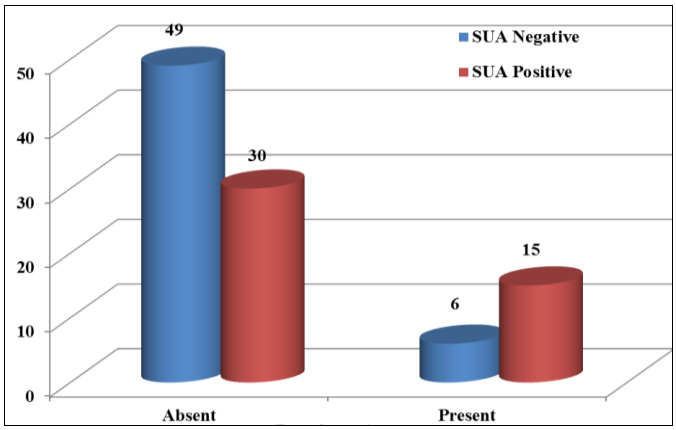

Fig 3: Preeclampsia

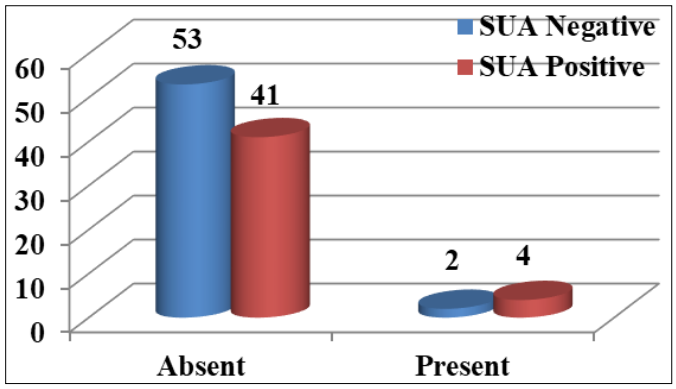

Fig 4: IGUR

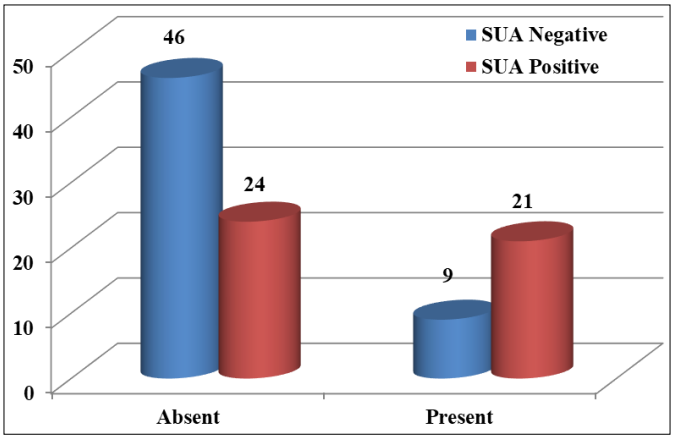

Fig 5: NICU Care

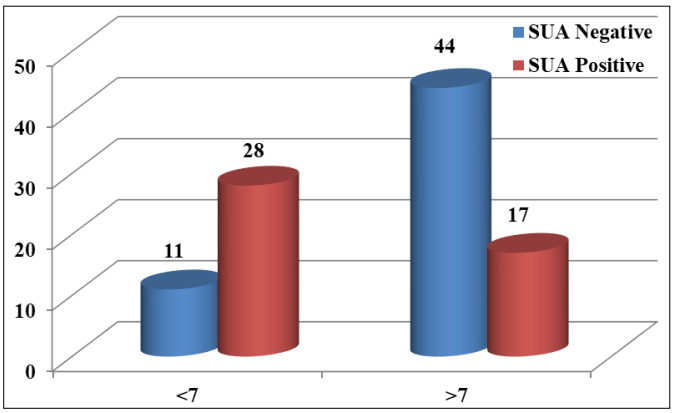

Fig 6: Apgar score at 1 min

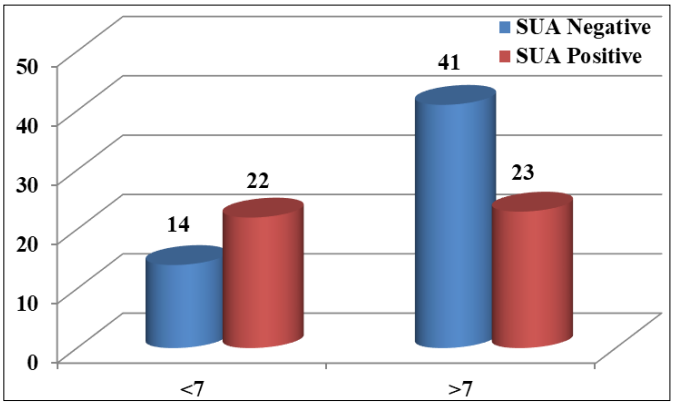

Fig 7: Apgar score at 5 min

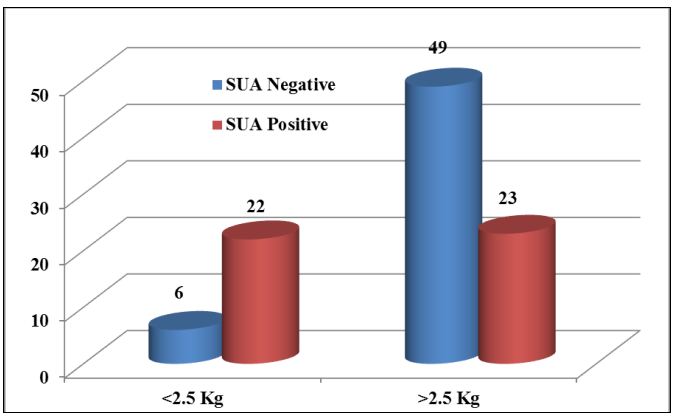

Fig 8: Birth weight

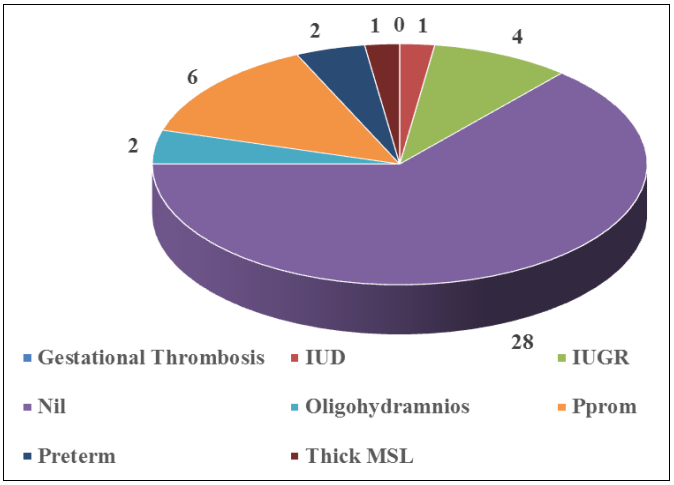

Fig 9: Complication based on Serum Uric Acid (Positive)

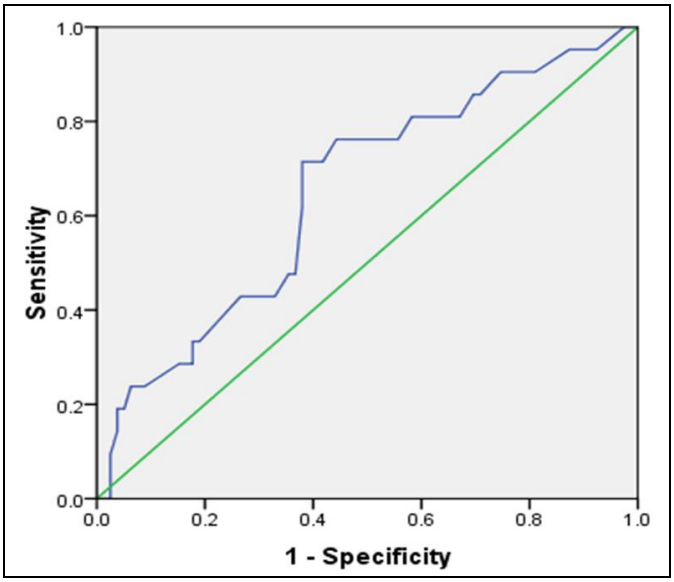

Fig 10: Roc Curve

Table 11: Area Under the Curve

Test Result Variable(s):Serum Uric Acid			
Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
.067	.035	.518	.781

Discussion

In present study among 100 pregnant women, maximum number of patients belong to age group 26 to 30yrs 42 (42%) followed by 28(28%) and 22 (22%) between age group 21 to 25yrs and >30 years respectively. Among 8 patients <20 years age,6(75%) had positive uric acid test, the P value is 0.013 which is statistically significant.

Obstretic index among the study subjects, both in uric acid test positive and negative group belong to primigravida are 13 (28.9%) and 32 (71.1%), among Gravida 2 are 22(53.7%) and 19(46.3%), among Gravida 3 are 7(77.8%) and 2(22.2%), among Gravida 4 are 3(75%) and 1(25%),among Gravida 5 are 0(0%) and 1(100%) respectively.

In our study, for 100 pregnant women the serum uric acid analysis was done. 45 patients were positive (where uric acid level is >_ 4.2mg/dl), Out of 21 patients who developed preeclampsia,15(71.4%) had positive serum uric acid

test(>_4.2mg/dl) and 6(28.6%) had negative uric acid test(<_4.2mg/dl), preeclampsia was absent in 79 women of which 30(38%) had uric acid test positive and 49(62%) had uric acid test negative. The p value is 0.006 which is statistically significant.

In present study among 100 study patients, out of 6 women who delivered IUGR babies,4(66.7%) had positive uric acid test and 2(33.3%) had negative uric acid test, among 94 women who did not have IUGR babies,41(43.6%) had uric acid test positive and 53(56.4%) had uric acid test negative. The P value is 0.271 which is statistically not significant. Our study does not correlates with the study of MARYAM ASGHAMIA. M.D., *et al*. In present study among 100 study patients, out of 39 who had APGAR score at 1min <7, 28(71.8%) babies had positive maternal serum uric acid test and 11(28.2%) had negative maternal serum uric acid test. Among 61 babies who had APGAR score at 1 min >7, 17(27.9%) had positive maternal serum uric acid test and 44(72.1%) had negative maternal serum uric acid test. The P value is 0.000 which is statistically significant. Present study correlates with CIMONA LYN SALDANA *et al*. study.

In present study among 100 study patients, out of 28 low birth weight babies(<2.5kg),22(78.6%) had positive maternal serum uric acid test and 6(21.4%) had negative maternal serum uric acid test. Among 72 babies who had birth weight>2.5kg,23(31.9%) had positive maternal uric acid test and 49(68.1%) had negative maternal uric acid test. The P value is 0.000 which is statistically significant. The study correlates with CIMONA LYN SALDANA et,al 2018 study, where birth weight of new born babies was average of <_ 2.5kg.

In our study, On applying ROC Curve to check the Diagnostic ability of the Serum Uric Acid level in predicting the Occurrence of Pre eclampsia was found to be statistically significant with p value of 0.0001 and the area under the curve to be 0.650. For the Cut of value of 4.2mg/dl of serum uric acid the Sensitivity was found to be 66.7% and Specificity was 10.9%.

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