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Study Of 24-Hour Urinary Protein Levels In Patients Of Preeclampsia Presenting To The Tertiary Care Center And Its Relation To Reduced EF And Development Of PPCM

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Abstract
Introduction: *Peripartum cardiomyopathy is very similar to other forms of non ischemic dilated cardiomyopathy except it's unique relation to pregnancy. It is a diagnosis of exclusion. Preeclampsia is a pregnancy specific syndrome that can affect virtually every organ system and is much more than gestational hypertension and proteinuria.*
Method: *This cross-sectional study was conducted at SRN hospital MLN medical college; a tertiary care centre, Prayagraj (U.P) India to study 24hour urinary protein levels in patients of preeclampsia presenting to the tertiary care center and it's relation with reduced EF and development of PPCM.*
Result: *A total of 200 pregnant females were screened for diagnosis of preeclampsia by diagnostic criteria given by American college of obstetrician and gynecology. Subjects underwent blood investigations and it was ensured no previous heart disease was present. BNP of the subjects was measured and echocardiography was done to establish the diagnosis of reduced EF (<45%) and peripartum cardiomyopathy in subjects. Reduced EF of <45% was found in 15.5% of PE patients even though most of them were asymptomatic for heart failure symptoms. Mean BNP levels in this group was 1946.96+-1307.77 pg/ml which was higher than the mean in group with EF>=45% which was 165.52+-83.07pg/ml .Overall PE patients having normal EF had mean BNP levels of 165.52+-83.07pg/ml . 24 hour urinary protein was measured. Mean Urinary Protein was 1549.31±698.16mg/24hr and median was 1400 mg/24hr. 24 urinary protein was significantly negatively correlated with EF (p value = 0.016) ,r=-0.241. Keeping an arbitrary cut off of 2grams for 24 hour urinary protein, in the subjects who had developed PPCM, 19 (61.3%) had urine protein less than 2000 mg/24hr and 12 (38.7%) had urine protein more than 2000 mg/24hr. The difference was found significant (p value= 0.018).*
Conclusion: *It has observed that patient with preeclampsia had higher prevalence of reduction in EF thereby making diagnosis of peripartum cardiomyopathy more in PE patients. Severity of proteinuria was found to be significantly correlated with reduction in EF and risk of development of PPCM. Hence severity of proteinuria can be used as a marker for cardiovascular involvement in preeclampsia patients.*
Keywords: *Peripartum cardiomyopathy , Preeclampsia ,BNP,EF,24 hour urinary protein*

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I. Introduction

Peripartum cardiomyopathy (PPCM), also called postpartum cardiomyopathy, is an uncommon, fatal cardiomyopathy of unknown etiology that affects women in the last month of pregnancy or within the first five months of the postpartum period.[1] Most frequently, it happens soon after birth. It is a rare condition that can carry mild or severe symptoms. The clinical features of PPCM are similar to any other heart failure and are due to LV systolic dysfunction like dyspnea, edema, fatigue etc. It can also present as shock, arrythmia, stroke secondary to left ventricular failure. Similar complaint like pedal edema and orthopnea are present in normal pregnancy hence the diagnosis is missed at times and it is diagnosed late.[2]It is known to spontaneously resolve hence mild cases are usually missed and correct incidence is difficult to be known. Out of the patients receiving normal medical therapy 50 percent recover to have normal EF but there are chances of reoccurrence. Some patients may experience progressive heart failure. The frequency of PPCM varies greatly from 1:100 to 1:10, 000 live births according to the ethnic, racial, and geographic background of the mother [3], with rates as high as 1 in 100 deliveries in Nigeria [4] and 1 in 300 deliveries in Haiti [5], to as low as 1 in 20, 000 deliveries in Japan [4].

In the United States, the reported incidence ranges from 1 in 1, 000 to 1 in 4, 000 [5-7]. It may be increasing due to the rise in maternal age, increased rates of multifetal pregnancies due to contemporary fertility techniques, and possible disease recognition. Many cases may, moreover, be unrecognized; thus, the actual incidence is unknown. Preeclampsia is a severe progressive multisystem disorder diagnosed by hypertension accompanied by any one of the following: proteinuria, BP of 160/110 mm Hg or higher despite bed rest, thrombocytopenia, impaired liver function, progressive renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbance. Preeclampsia is responsible for 15% of maternal deaths. The cause of preeclampsia, though not entirely clear, can be endothelial dysfunction that causes abnormal remodeling of the placental spiral arteries .Hypertension is just one feature of the diffuse endothelial dysfunction, which is associated with vasospasm, reduced end-organ perfusion, and activation of the coagulation cascade. Preeclampsia tends to occur more commonly in nulliparous women; in women with a body mass index of more than 30 kg/m2 ; age older than 40 years; preexisting medical conditions (renal disease or pregestational diabetes mellitus, systemic lupus erythematosus, or antiphospholipid antibody syndrome); or a history of preeclampsia, fetal growth restriction, or placental abruption; and in those conceiving after assisted reproductive techniques, with multifetal pregnancies. Hypertension usually does not develop until the second half of gestation, sometimes accompanied by new-onset significant proteinuria (excretion of 3 g of protein over 24 hours) and maternal organ dysfunction or uteroplacental dysfunction.

A 2013 meta-analysis of 22 studies found a 22% prevalence of PE among women with PPCM, more than four times the estimated global prevalence [6]. Similarly, of the first 411 women in the EURObservational Research Programme PPCM registry, 22.8% had PE [7]. Owing to the heterogeneity of studies performed to date and limitations of data available from Africa and the Caribbean [6], it is unclear whether the association between PPCM and PE differs between black women, who have higher rates of both conditions, and women of other racial and ethnic backgrounds. Since the publication of these seminal studies, PE has often been cited as an independent risk factor for developing PPCM[8,9], but not all clinical studies support this conclusion [10].

Recent research suggests that PPCM is a vascular disease triggered by late–gestational secretion of potent antiangiogenic agents from the placenta and pituitary [11, 12]. In this context, the frequently noted association of PPCM with PE is of particular interest because PE is similarly caused by excess secretion of such antivascular factors from the placenta [13]. Multiple gestations also have higher circulating levels of these antiangiogenic factors and are a risk factor for PPCM and PE [14, 15].

II. Materials and method

Study Design: This Prospective Cohort (observational) study was conducted in SRN Hospital, MLN Medical College, Prayagraj, Uttar Pradesh, India from July 2021 to August 2022 on 200 patients of preeclampsia.

Case Selection: Patients presenting between last month of pregnancy and 5 months post-partum with suggestive symptoms and confirmed by physical examination and biochemical tests for pre-eclampsia were selected randomly from obstetrics and gynaecology emergency IPD and OPD, Medicine IPD and OPD and Cardiology IPD and OPD of SRN Hospital, MLN Medical College, Prayagraj, Uttar Pradesh, India.

Inclusion Criteria

- Women in last month of pregnancy till 5-month post-partum diagnosed as preeclampsia.
- Women with no prior history of heart disease.
- Women giving consent for the study.

Exclusion Criteria

- Women with prior history of heart disease.
- Women with heart failure developing before last month of pregnancy.
- Women with history of hypertension developing before 20 weeks of gestation.
- Those unwilling for study related diagnostic procedures.

After obtaining informed consent and fulfilling inclusion and exclusion criteria, demographic characteristics and details, the diagnosis of preeclampsia was ascertained. An echo was done at the time of enrollment and only women with normal echo were enrolled in the study.

Following blood and radiological investigations were required – CBC, LFT, KFT, S.electrolytes, TSH, urine routine and microscopy, 24 hour urinary protein.

Patient confirmed with pre-eclampsia were evaluated further with BNP and 2D ECHO done anywhere between third trimester till discharge. Patients having derangement in these two investigations underwent trop I to rule out other causes of derangement.

A Chest X Ray was done in post-partum period.

III. Results

A total of 200 PE patients were included in the study with diagnostic criteria as described in materials and method. Mean age of study sample was 27.71±3.85 years and median was 28 years. Subjects were in the age range of 19 to 37 years.

Out of 200 patients enrolled 31 patients i.e.15.5% were found to have EF <45%.

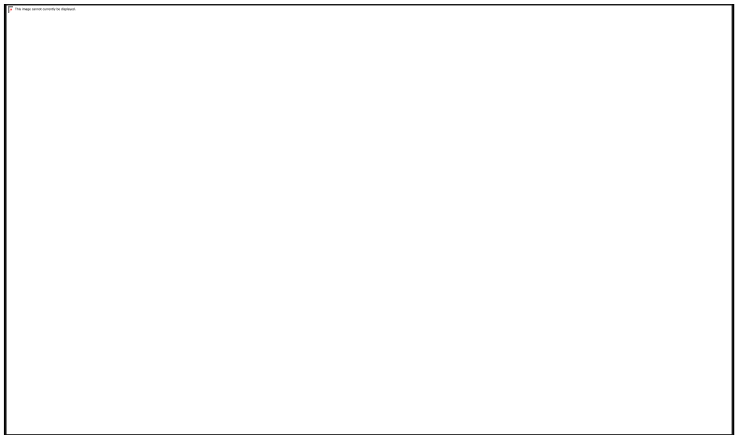

Figure1: Development of PPCM in PE patients

	Mean	**SD**	**Median**	**Min**	**Max**	**Valid N**
EF(%)	55.10	10.84	58.00	20.00	68.00	200

Table1: Description of BNP in study population.

Table 1 shows the description of EF of study population. Mean EF was 55.1±10.84% and median was 58%. Subjects were in the range of 20 to 68%

	Mean	**SD**	**Min**	**Max**	**Valid N**
In patients with EF>=45%	165.52pg/ml	83.07 pg/ml	29 pg/ml	606 pg/ml	**169**
In patients with EF<45%	1946.93 pg/ml	1309.77 pg/ml	296 pg/ml	4980 pg/ml	**31**

Table 2: Description of BNP in accordance with EF with 45% as cut off

Table 2 shows the description of BNP (pg/ml) of study population in accordance with EF with cut off of EF as 45%. Mean BNP was 1946.93+/-1309.77pg/ml in patients fulfilling the diagnostic criteria for PPCM with EF<45%. Subjects were in the range of 296 to 4980pg/ml. Mean BNP was 165.52 pg/ml in patients having EF≥45%. Subjects were in the range of 29 to 606 pg/ml.

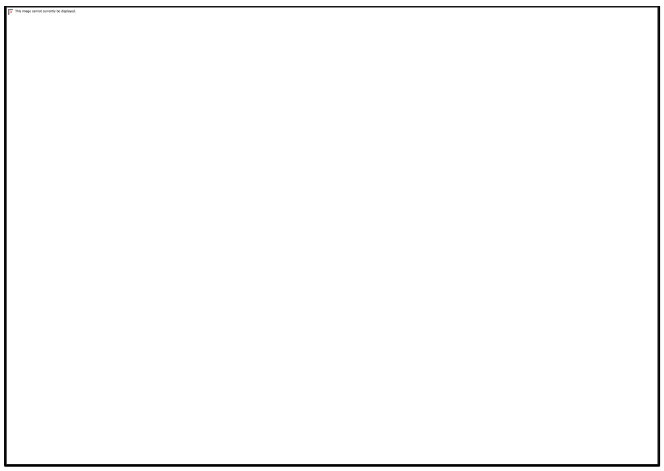

Figure 2: Correlation of BNP with EF

Figure 2 shows the correlation of BNP with EF. The above said correlation was a significant (p-value =

negative correlation with r=-0.334.

	Mean	**SD**	**Median**	**Min**	**Max**	**Valid N**
Urinary Protein (mg/24hr)	1549.31	698.16	1400.00	560.00	4860.00	200

Table 3: Description of 24 hour urinary protein in study population

Table 3 shows the description of Urinary Protein of the study population. Mean Urinary Protein was 1549.31±698.16mg/24hr and median was 1400 mg/24hr. Subjects were in the range of 560 to 4860 mg/24hr.

	Development of PPCM						**Mann Whitney U test**	
	EF<45%		**EF >=45%**		**Total**		**Z value**	**p-value**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Urinary Protein 24hr(mg/24hr)	1903.48	881.31	1484.34	641.31	1549.31	698.16	-2.677	**0.007**

Table 4: Description of 24 hour urinary protein in the two subgroups.

			EF	**Urinary Protein 24hr**
Spearman's rho Correlation Coefficient	EF		1.000	-.241*
		Sig. (2-tailed)	.	**.016**
		N	200	200
*. Correlation is significant at the 0.05 level (2-tailed).				

Table 5: Correlation of EF with urinary protein

Above table 5 shows the correlation of EF with 24 urinary proteins. The above-said correlation was significant (p-value = 0.016) negative correlation with r=-0.241.

Figure 3: Correlation of EF with urinary protein

24 hr Urine Protein	Frequency	%
<=2000 (mg/24hr)	155	77.5
>2000 (mg/24 hr)	45	22.5
Total	200	100.0

Table 6: Distribution of urine protein in the study population

Table 6 shows the distribution of urine protein in the study population with an arbitrary cut off of 2gm/24 hours. 77.5% had urine protein less than or equal to 2000 mg/24hr while 22.5% had more than 2000 mg/24hr

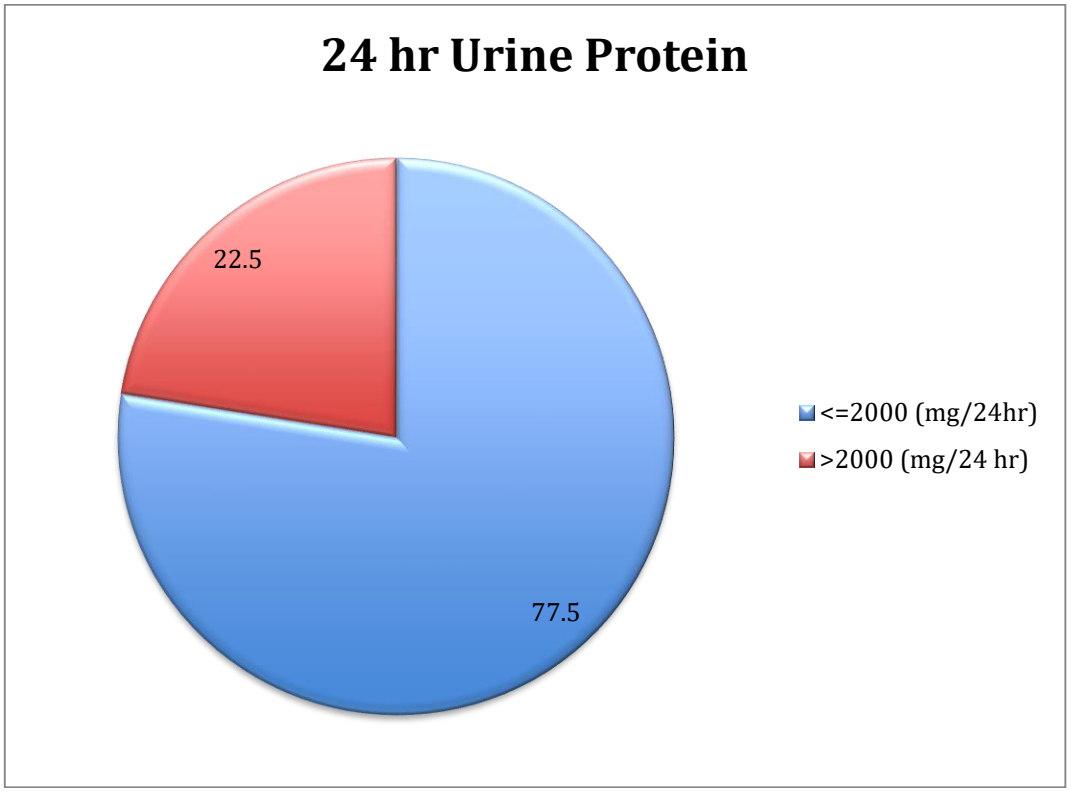

Figure 4: Distribution of urinary protein in study population (in %).

Urine Protein	Development of PPCM					
	EF<45%		EF >=45%		Total	
	N	%	N	%	N	%
<=2000mg/24hr	19	61.3%	136	80.5%	155	77.5%
>2000mg/24hr	12	38.7%	33	19.5%	45	22.5%

Table 7: Applied χ^2 test for significance. χ^2 value=5.53; df=1; p-value=0.018; consider significant.

Above table 7 shows the association of 24hr urinary protein with development of PPCM in the study population. In the subjects who had developed PPCM, 19 (61.3%) had urine protein less than 2000 mg/24hr and 12

(38.7%)had urine protein more than 2000 mg/24hr. The difference was found significant (p value= 0.018).

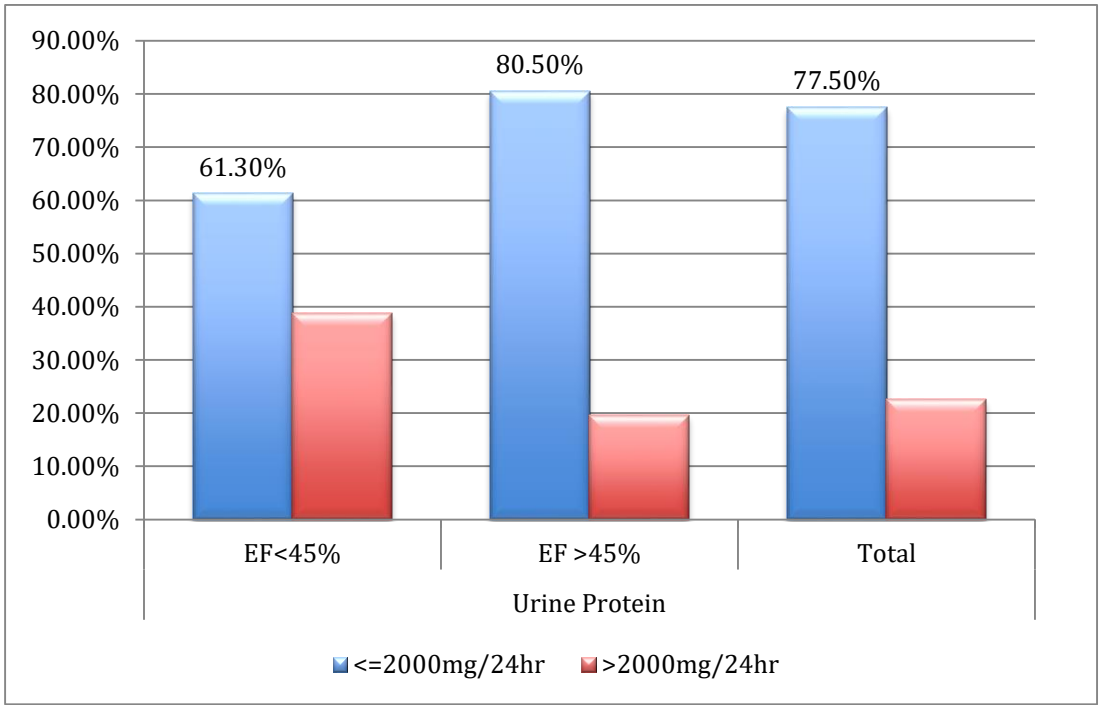

Figure 5: Distribution of EF in relation to 24 hrs urinary protein

Table 8: Mortality in study population

		%
Total mortality	**8**	**4%**
Mortality in study population with normal EF	**4**	**2%**
Mortality in study population with EF<45% with non cardiac cause of death	**2**	**1%**
Mortality in study population with EF<45% with established cardiac cause of death	**2**	**1%**

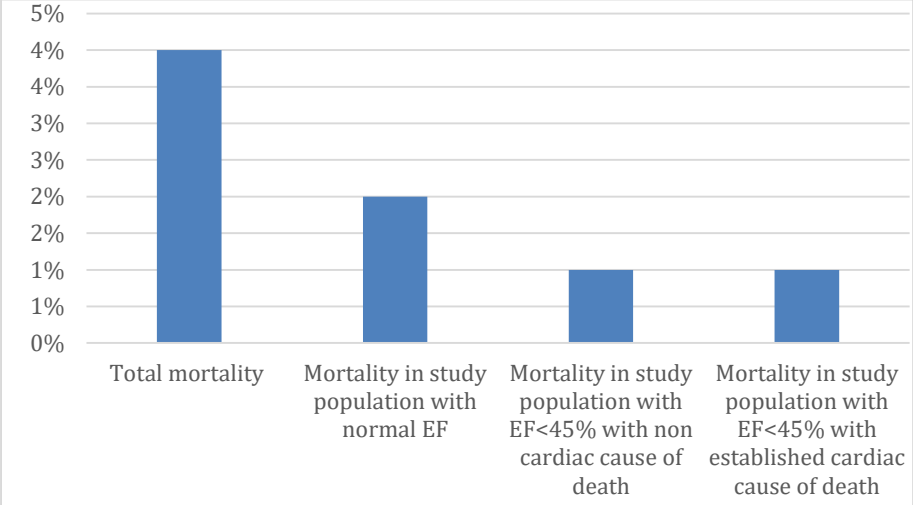

Figure 6: Mortality in study population

Table 9:Mortality in group of patients with reduced EF (EF <45%)

Total patients	**31**	
Total mortality in subgroup	**4**	**12.9%**
Mortality due to non cardiac cause	**2**	**6.4%**
Mortality due to established cardiac cause	**2**	**6.4%**

There were 8 mortalities in the study population (table 8). Out of these 8, 4 mortalities were in the group of patients who had EF >45% and the cause of mortality ranged from post op complications to neurological complications . 4 patients were in the group of patients having EF <45% (table 9) 2 out of these 4 had no heart failure related symptoms and the cause of death was not established to be cardiac. Other 2 had established cardiac cause of death which were pulmonary edema in one patient and cardiogenic shock in other patient.

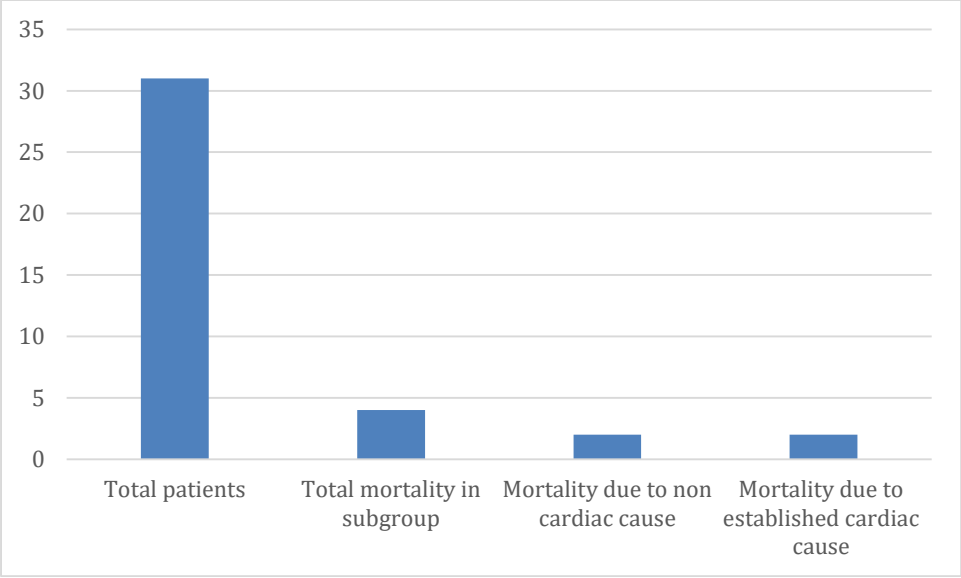

Figure 7: Mortality in group of patients with reduced EF (EF <45%)

IV. Discussion

This prospective cohort (observational) study was done on a total of 200 women at MLN Medical College, Prayagraj, Uttar Pradesh, India, with a mean age of 27.71±3.85 years. The mean BNP (pg/ml) was 441.64±825.93, and the median was 210, which is consistent with other studies which reported increased levels of BNP and NT-proBNP in pre-eclampsia[16,17,18]. High values of BNP in pre-eclampsia reflect pathophysiological changes in left ventricular mass and volume [19]. BNP, or N-terminal pro-brain natriuretic peptide (NTproBNP) levels are helpful to screen potential PPCM patients. Patients with acute PPCM have consistently elevated plasma concentrations of natriuretic peptides, BNP or NT-proBNP .

Our study showed a significant negative correlation of BNP with EF. Increased BNP levels were associated reduced EF. (p value <0.001)

Echocardiography findings in the study population confirm the that 31 (15.5%) had EF<45% even though most were asymptomatic for heart failures symptoms and 169 (84.5%) had EF >= 45%. This data showed significantly higher cardiac involvement in preeclampsia patients than expected. It may be due to the fact that normal pregnancy symptoms like pedal edema and dyspnea overlap with mild symptoms of heart failure and hence diagnosis is missed.

In the present study, TSH, hemoglobin, and platelet among preeclampsia subjects were negatively correlated with BNP (r= -0.165. -0.030, and -0.294, respectively), while TLC was positively correlated with BNP (r= 0.247). TSH, TLC, and platelet were significantly associated with BNP (p values = 0.019, <0.001, and <0.001, respectively).

The correlation of bilirubin, ALP, SGOT, SGPT, S. urea, and S. creatinine with BNP was significantly positive in our study among preeclampsia subjects, with r= 0.307, 0.466, 0.151, 0.202, 0.387, and 0.404, respectively.

In our study, among preeclampsia patients, 155 (77.5%) had 24 hour urine protein ≤ 2000 mg/dl, while 45 (22.5%) had 24 hour urinary protein >2000 mg/dl. Of the subjects, who had developed PPCM, 19 (61.3%) had urine protein less than 2000 mg/dl, and 12 (38.7%) were more than 2000 mg/dl. The difference was found to be significant (p-value= 0.018). Proteinuria is associated with preeclampsia though it is not essential for diagnosis of PE. It is due to widespread endothelial dysfunction in preeclampsia probably due to anti angiogenic factors. Further studies are required to prove association between proteinuria severity and disease severity in preeclampsia though it has been found to be associated with preterm deliveries. Why severity of proteinuria is associated with more cardiac dysfunction presenting as decreased ejection fraction is not clear but in our study 24 hour urinary protein was inversely proportional to ejection fraction. Further studies are required to show the pathophysiology behind this finding. It can lead to the use of 24 hour urinary protein as a marker to hint towards more cardiovascular involvement in PE patients and help in screening such patients so that they can be diagnosed and if cardiac involvement is found, they can be counselled about the risks in next pregnancy.

V. *CONCLUSION*

This prospective cohort (observational) study was done on 200 women with a mean age of 27.71±3.85 years. Echocardiographic findings confirm the diagnosis of reduced EF of less than 45% in last month of gestation till 5 month postpartum in 31 females (15.5%) and mean BNP level of study population was 441.64pg/ml. Mean BNP of patients having reduced EF (<45%) was 1946.96pg/ml and mean BNP of patients with normal EF(>=45%) was 165.52pg/ml. A significant negative correlation of BNP with EF was found (p value < 0.001). Mean Urinary Protein was 1549.31±698.16mg/24hr and median was 1400 mg/24hr. Subjects were in the range of 560 to 4860 mg/24hr. 24 hour urinary protein was significantly negatively correlated with EF (p value = 0.016) with r=-0.241.

Among preeclampsia patients, taking an arbitrary cut off of 2grams urinary protein/24 hours,77.5% had urine protein ≤ 2000 mg/24hr, while 22.5% had >2000 mg/24hr. Of the subjects, who had developed PPCM, 19 (61.3%) had urine protein less than 2000 mg/24hr, and 12 (38.7%) had more than 2000 mg/24hr. On applying statistical tests, 2gm value of 24 hour urinary protein was associated with reduced EF of less than 45% with p value of 0.018 which was statistically significant.

Hence the study showed 24 hour urinary protein can be used as an investigation to predict cardiovascular involvement in PE patients and with a cut off of 2 grams for 24 hour urinary protein, patient can be selected to undergo special cardiac investigations like BNP and 2D echocardiography to find out such patients and prevent mortality and morbidity in present and future pregnancies.

VI. LIMITATIONS

A major limitation of study was small size of study population which limits the power of statistical tools. As ours was a tertiary center most of the patients presenting to our center were of complicated pregnancy which can lead to a higher incidence of cardiac involvement.

Also , it was a uni-centric study. A multi-centric study would have given a better result.

We were not able to follow up the patients after discharge hence long term outcomes were not clear.

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