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Original Article

Obstetrics and Gynaecology Section

Role of Cerebro-Placental Ratio in Predicting Adverse Outcomes in Low-risk Pregnancies- A Prospective Cohort Study

C KAVYARANI[1], RAVI N PATIL[2], C SATHYAVANI[3], SHINY VARGHESE[4]

ABSTRACT

Introduction: Abnormal Cerebro-Placental Ratio (CPR) is associated with a substantial risk of adverse perinatal outcomes and the test seems to be particularly useful for follow-up of foetuses with sonographically diagnosed Foetal Growth Restriction (FGR).

Aim: To determine the usefulness of doppler velocimetry, especially CPR at 35 weeks of gestation or later, in predicting intrapartum foetal heart rate abnormalities and adverse neonatal outcomes in low-risk term pregnancies.

Materials and Methods: The present prospective cohort study was conducted at the Department of Obstetrics and Gynaecology in Bangalore Baptist Hospital, Bangalore, India from September 2019 to September 2020. A total of 60 pregnant women between the age group of 18 to 35 years with low-risk pregnancies, who present for the obstetrical ultrasound at 35 weeks of gestation or later with planned delivery at the hospital were included. All low-risk pregnant women with Estimated Foetal Weight (EFW) >10th centile and abnormal Cerebro-Placental Ratio (CPR) <10th centile were compared with those of normal CPR i.e., >10th centile. An adverse obstetric outcome like foetal distress, meconium aspiration syndrome or respiratory distress syndrome, mode of delivery, admission to Neonatal Intensive Care Unit (NICU), and perinatal mortality was analysed in the study population using Chi-square test or Fisher's-exact test.

Results: In this study, there was a significant association between foetal distress and CPR with Odds Ratio (OR) of 4.21 i.e., foetal distress was 4.21 times higher in the abnormal group compared to the normal group. Among 20 cases with abnormal CPR, 11 had foetal distress i.e., 55% and among 40 cases with normal CPR, nine had foetal distress i.e., 22.5%. Among those with abnormal CPR, 15% had Amniotic Fluid Index (AFI) <8 and among those with normal CPR, 0 had AFI <8, showing a significant association.

Conclusion: In low-risk patients with EFW >10th centile and abnormal CPR, there was a significant association with adverse obstetric outcomes, requiring vigilant intrapartum monitoring.

Keywords: Adverse obstetric outcome, Amniotic fluid index, Adverse obstetric outcome, Doppler, Meconium aspiration syndrome, Neonatal outcome foetal distress

INTRODUCTION

Foetal hypoxia in the intrapartum period may result in adverse perinatal outcomes including neurologic injury, seizures (neonatal encephalopathy), and death [1]. Uterine contractions in labour are associated with a 60% reduction in placental blood flow and whilst the majority of foetuses are able to cope with this lower perfusion, those that are unable to do so are at risk of intrapartum hypoxia [2].

Ultrasound doppler studies are usually used during pregnancies complicated by FGR, to help in their management. But it can also be used in predicting adverse outcomes in low-risk pregnancies. These growth restricted foetuses are known to have intrapartum compromise. But now studies have shown that even normally grown foetuses are also at high-risk of intrapartum compromise, which is because of cerebral redistribution of foetal blood as seen in other foetal growth restricted foetuses [3,4].

Recently, there has been a debate regarding the definition of FGR, with some authors suggesting a more appropriate definition of FGR would be the presence of a low CPR {ratio of the foetal Middle Cerebral Artery Pulsatility Index (MCA PI) to the Umbilical Artery Pulsatility Index (UA PI)}, rather than solely foetal weight. This is because a definition based purely on size may fail to identify a foetus whose estimated weight is >10th centile but may indeed have suboptimal growth and thus, a failure to reach its genetic growth potential [5].

There have been few studies conducted in this field. Ropacka-Lesiak M et al., concluded that the CPR ratio shows the highest sensitivity in predicting FHR abnormalities and adverse neonatal outcomes in uncomplicated pregnancies those at 40 weeks and beyond [1]. Similarly, a study conducted by Bligh LN et al., concluded that the CPR 10th centile resulted in the best screening performance, the CPR 10th centile may be useful as part of a risk stratification tool for the prediction of low birth weight and adverse intrapartum and neonatal outcomes [5].

Cerebral redistribution in these foetuses is reflected by a low CPR which is now believed to be a reliable surrogate marker of suboptimal foetal growth. It gradually rises until around the 34th week of gestation, and subsequently slowly declines until term. Increased cerebral blood flow is a foetal adaptive response to hypoxia and this is reflected by a reduction in MCA resistance (decreased PI) and thereby a reduction in the CPR [4,6]. CPR is the blood flow index which will predict the phenomenon of cerebral redistribution in the foetus. A decline in the values of CPR can either result from the rise in vascular resistance in umbilical artery, which reflects the placental resistance changes or be a consequence of the Brain Sparing effect arising from the fall in cerebral vascular resistance [7].

Many adverse obstetric and neonatal outcomes like low birth weight, operative delivery, meconium-stained liquor, non reassuring foetal heart rate patterns, low Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) scores, acidosis, Neonatal Intensive Care Unit (NICU) admission and perinatal mortality are seen in foetuses with a low CPR of less than 10th percentile. CPR has been shown to be a good predictor of the foetal oxygenation status at birth and can be used to identify pregnancies that are at risk for adverse outcomes [1].

Studies suggest that CPR is more effective in predicting adverse perinatal outcomes compared with the individual doppler parameters

of MCA and UA. Thus, CRP assumedly reflects haemodynamic changes and blood flow redistribution more accurately than the umbilical or cerebral flows assessed separately [7-9].

Estimated foetal weight may not predict the foetal outcome because of the wide variation in normal range, but CPR provides an objective reference. A more accurate screening approach to identify foetuses that fail to reach their genetic growth potential is needed particularly in low-risk pregnancies. This study was done to determine the usefulness of doppler velocimetry, especially CPR at 35 weeks of gestation or later, in predicting intrapartum foetal heart rate abnormalities and adverse neonatal outcomes in low-risk term pregnancies.

MATERIALS AND METHODS

The present prospective cohort study was conducted at the Department of Obstetrics and Gynaecology at Bangalore Baptist Hospital, Bangalore, India, which is a 340-beded NABH accredited tertiary care center with Diplomate of National Board (DNB) training program from September 2019 to September 2020. Institutional Ethical clearance was obtained with IEC number- BBH/IRB/2019/042.

Inclusion criteria: Low-risk pregnant women between the age group of 18 to 35 years, who presented for the obstetrical ultrasound at 35 weeks of gestation or later with planned delivery at the hospital were included in the study.

Exclusion criteria: Multifoetal pregnancy at the time of presentation, foetal malformation, pre-eclampsia, FGR (EFW <10th centile), prior cesarean section, and placental abnormalities such as previa or accreta were excluded from the study.

Sample size calculation: Based on the epidemiological sample size formula using the hypothesis testing of the relative risk, the proportion of abnormal Cardiotocography (CTG) in the normal CPR group was 0.19 and anticipated relative risk was 3. The proportion of abnormal CTG in the abnormal CPR group was 0.57 and with an allocation ratio of 1:2, at 80% of power and 5% of alpha error, the estimated sample size for the exposed group was 19 and in the unexposed group, it was 38 [1]. Hence, in the present study total sample collected was 60, among the exposed group 20 subjects, and in the unexposed group, 40 subjects were enrolled and studied.

After proper counseling, informed written consent was obtained from low-risk pregnant women, detailed history was taken and clinical examinations were performed. All the antenatal women were examined by transabdominal ultrasound scan and colour doppler using a standard ultrasound machine. Subsequently, doppler indices were calculated by taking average values of atleast four consecutive waveforms. Low-risk pregnancies were defined as a clinical scenario for which there is no demonstrable benefit for intervention. All low-risk pregnant women with EFW >10th centile and abnormal CPR <10th centile were compared with those with normal CPR i.e., >10th centile.

Adverse perinatal outcomes studied were foetal distress evidenced by foetal bradycardia or persistent tachycardia requiring cesarean section or instrumental delivery, meconium stained liquor, APGAR score of <6 at 5 minutes, neonatal complications like meconium aspiration syndrome or respiratory distress syndrome, admission to NICU, and perinatal mortality were analysed in the study population.

STATISTICAL ANALYSIS

Data was entered into a Microsoft Excel data sheet and was analysed using Statistical Package for the Social Science (SPSS) 22.0 version software. Categorical data was represented in the form of frequencies and proportions. The Chi-square test or Fisher's-exact test (for 2×2 tables only) was used as a test of significance for qualitative data. Continuous data was represented as mean and standard deviation. An Independent t-test was used as a test of significance to identify the mean difference between the two variables. Receiver Operating Characteristic (ROC) curve was made. The p-value of <0.05 was considered to be statistically significant.

RESULTS

In the present study, the study subjects were divided into two groups based on CPR into normal group and abnormal group. CPR >10th centile was considered as normal and CPR <10th centile as an abnormal group as per standard reference [5].

In the study, there was no significant association between CPR and gestational age, parity, age, and estimated foetal weight [Table/Fig-1]. Among those with abnormal CPR, 15% had AFI <8 and among those with normal CPR, 0 had AFI <8 [Table/Fig-2].

In the study, there was a significant association between foetal distress and CPR i.e., among those with abnormal CPR, 55% had foetal distress and among those with normal CPR, 22.5% had foetal distress [Table/Fig-3].

Among those with abnormal CPR, 3 babies weighed <2.5 kg, the lowest being 2.28 kg. All babies had good APGAR scores, >6 at 5 minutes. One baby got admitted to NICU for respiratory distress, with NICU stay being <24 hours. In the study, there was no significant difference in neonatal outcome and CPR. Perinatal mortality was not observed in this study [Table/Fig-4]. In the study, there was no significant association between overall obstetric and neonatal outcome with respect to CPR [Table/Fig-5].

Among subjects with abnormal CPR, 87.5% had abnormal obstetric outcome and among subjects with normal CPR, 69.4% had abnormal obstetric outcome. Among subjects with abnormal CPR, 16.7% had abnormal neonatal outcome and among subjects with normal CPR, 5.6% had abnormal outcome. There was no

Variables		CPR				p-value*	OR	95% Confidence interval
		Abnormal (<10th centile)		Normal (>10th centile)				
		Count	%	Count	%			
Gestational age	≤40 weeks	18	90%	29	72.5%	0.121	0.292	0.058, 1.476
	>40 weeks	2	10%	11	27.50%			
Parity	Primigravida	15	75%	26	65%	0.432	0.619	0.186, 2.061
	Multigravida	5	25%	14	35%			
Age	≤30 years	16	80%	33	82.50%	0.814	1.179	0.3007, 4.619
	>30 years	4	20%	7	17.50%			
Estimated foetal weight	<2.5 kg	3	15%	11	27.50%	0.281	0.465	0.1136, 1.905
	≥2.5 kg	17	85%	29	72.50%			

[Table/Fig-1]: Association between CPR and demographic profile of subjects.
*Chi-square test

Variable		CPR: Abnormal (<10th centile) Count	CPR: Abnormal (<10th centile) %	CPR: Normal (>10th centile) Count	CPR: Normal (>10th centile) %	p-value*
Amniotic Fluid Index (AFI)	<8	3	15.0%	0	0%	0.012

[Table/Fig-2]: Association between CPR and Amniotic Fluid Index (AFI).
*Independent t-test

significant association between CPR at 1.5 cut-off and obstetric outcome and neonatal outcome [Table/Fig-6].

CPR value of ≤1.52 was the cut-off in differentiating abnormal and normal obstetric outcome as stated by Younden's index. CPR at ≤1.52 had had highest sensitivity of 52.17%, specificity of 78.57%, PPV of 88.9% and NPV of 33.3% in predicting abnormal obstetric outcome [Table/Fig-7-9].

CPR value of ≤1 was the cut-off in differentiating abnormal and normal neonatal outcome as stated by Younden's index. CPR at

Variables		CPR: Abnormal (<10th centile) Count	CPR: Abnormal (<10th centile) %	CPR: Normal (>10th centile) Count	CPR: Normal (>10th centile) %	p-value*	OR	95% CI
Foetal heart tracings	Reassuring	11	55%	28	70.00%	0.251	1.909	0.6288, 5.796
	Non reassuring	9	45%	12	30.00%			
Induction	Yes	16	80%	22	55.00%	0.058	0.306	0.08665, 1.078
	No	4	20%	18	45.00%			
Mode of delivery	Vaginal	11	55%	25	62.50%	0.855	1.286	0.3894, 4.245
	LSCS	6	30%	10	25.00%			
	Instrument	3	15%	5	12.50%			
Foetal distress	Yes	11	55%	9	22.50%	0.012	4.21	1.331, 13.32
	No	9	45%	31	77.50%			
Liqour	Clear	15	75%	36	90.00%	0.125	3	0.7065, 12.74
	meconium	5	25%	4	10.00%			

[Table/Fig-3]: Association between obstetric outcome and CPR.
*Chi-square test with Yates correction

Variables		CPR: Abnormal (<10th centile) Count	CPR: Abnormal (<10th centile) %	CPR: Normal (>10th centile) Count	CPR: Normal (>10th centile) %	p-value*	OR	95% CI
Outcome	Live birth	20	100.00%	40	100.00%	-	-	-
APGAR-1	>3	20	100.00%	40	100.00%	-	-	-
APGAR-5	>6	20	100.00%	40	100.00%	-	-	-
Birth weight	< 2.5	3	15.00%	1	2.50%	0.067	6.882	0.6672, 70.99
	≥ 2.5	17	85.00%	39	97.50%			
NICU stay	No	19	95.00%	39	97.50%	0.611	2.053	0.1217, 34.62
	Yes	1	5.00%	1	2.50%			

[Table/Fig-4]: Association between neonatal outcome and CPR.
*Fisher-exact test

Variables		CPR: Abnormal (<10th centile) Count	CPR: Abnormal (<10th centile) %	CPR: Normal (>10th centile) Count	CPR: Normal (>10th centile) %	p-value*	OR	95% CI
Obstetric outcome	Normal	2	10%	12	30%	0.084	3.857	0.7712, 19.29
	Abnormal	18	90%	28	70%			
Neonatal outcome	Normal	16	80%	38	95%	0.068	4.75	0.7891, 28.59
	Abnormal	4	20%	2	5%			

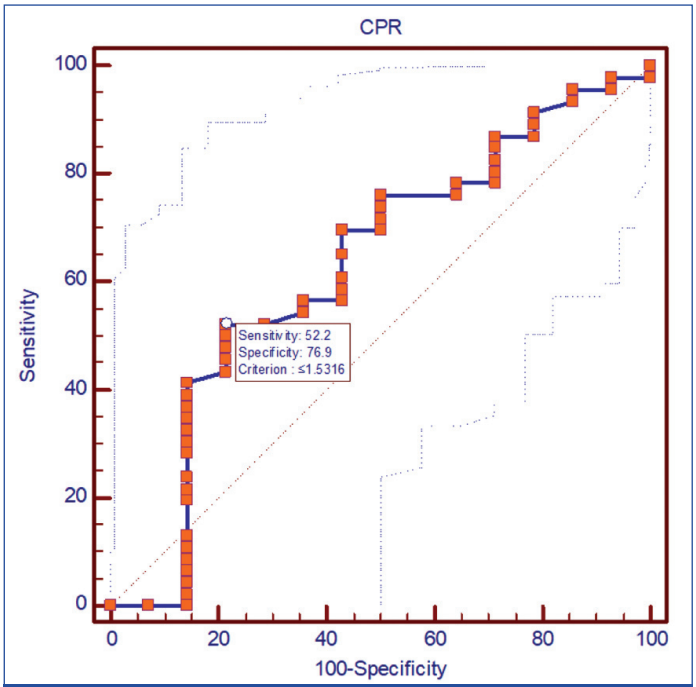
[Table/Fig-5]: Association of abnormal obstetric and neonatal outcome with CPR.
*Chi-square test

Variables		CPR: Abnormal (<1.5) Count	CPR: Abnormal (<1.5) %	CPR: Normal (>1.5) Count	CPR: Normal (>1.5) %	p-value*	OR	95% CI
Obstetric outcome	Normal	3	12.5%	11	30.6%	0.105	3.08	0.757, 12.52
	Abnormal	21	87.5%	25	69.4%			
Neonatal outcome	Normal	20	83.3%	34	94.4%	0.160	3.4	0.570, 20.26
	Abnormal	4	16.7%	2	5.6%			

[Table/Fig-6]: Association of abnormal obstetric and neonatal outcome with CPR.
*Chi-square test

Variables	Values
Area under the ROC curve (AUC)	0.627
Standard error	0.0931
95% Confidence interval	0.492 to 0.748
z statistic	1.359
Significance level P (Area=0.5)	0.1743
Youden index J	0.3075
95% Confidence interval	0.1832 to 0.4348
Associated criterion	≤1.52
95% Confidence interval	0.49 to 1.91

[Table/Fig-7]: Validity of CPR in predicting abnormal obstetric outcome.



[Table/Fig-8]: ROC curve showing validity of CPR in predicting abnormal obstetric outcome.

Criterion	Sensitivity	95% CI	Specificity	95% CI	+PV	95% CI	-PV	95% CI
≤1.53	52.2	36.9-67.1	76.9	49.2 -95.3	88.9	70.8-97.6	33.3	18.0 -51.8

[Table/Fig-9]: Criterion values and coordinates of the ROC curve.

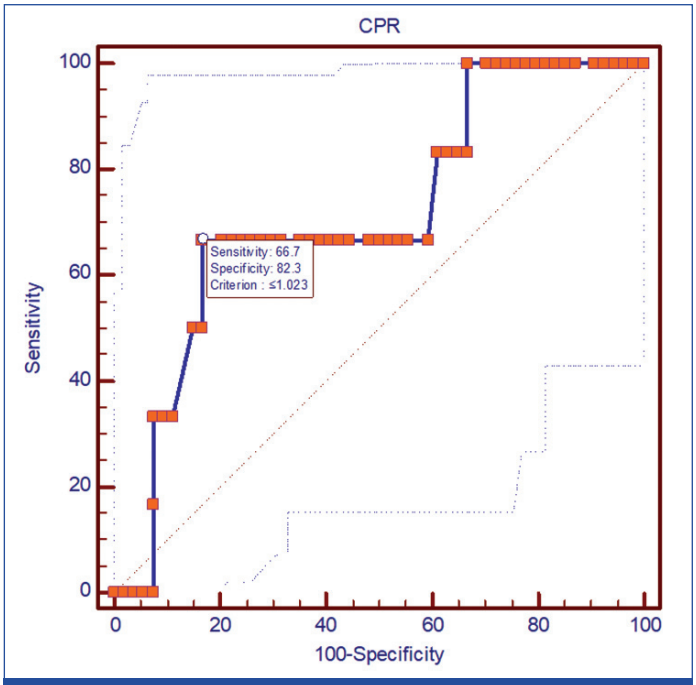
≤1 had had highest sensitivity of 66.67%, specificity of 83.33% in predicting abnormal neonatal outcome [Table/Fig-10-12].

Variables	Values
Area under the ROC curve (AUC)	0.715
Standard error	0.118
95% Confidence interval	0.583 to 0.824
z statistic	1.821
Significance level P (Area=0.5)	0.0686
Youden index J	0.5000
95% Confidence interval	0.2778 to 0.7963
Associated criterion	≤1
95% Confidence interval	0.71 to 1

[Table/Fig-10]: Validity of CPR in predicting abnormal neonatal outcome.

DISCUSSION

In the present study, the percentage of subjects with low AFI and foetal distress was higher in the group with abnormal CPR (<10) with significant p-value. Moreover, in the abnormal CPR group operative delivery, meconium stained amniotic fluid, LBW and admission to NICU was high but not statistically significant.



[Table/Fig-11]: ROC Curve showing validity of CPR in predicting abnormal neonatal outcome.

Criterion	Sensitivity	95% CI	Specificity	95% CI
≤1	66.67	22.3-95.7	82.3	70.7-92.1

[Table/Fig-12]: Criterion values and coordinates of the ROC curve.

From the studies by Ropacka-Lesiak M et al., conducted at the Department of Perinatology and Gynaecology, Poland from 2007 to 2009 and a prospective multicenter observational study conducted by Dall'Asta A at three tertiary centers in Italy between January 2016 to July 2017, similar findings were observed with respect to maternal and neonatal outcome as in the index study [1,10]. However, in a retrospective analysis conducted by Gruttner B et al., at the Department of Obstetrics and Gynaecology at the University Hospital of Cologne between 2011 to 2018, rate of LSCS was high in the study in both abnormal CPR and normal CPR [Table/Fig-13] [1,10,11].

Present study showed CPR value of ≤1.52 had highest sensitivity of 52.17%, specificity of 78.57%, PPV of 88.9% and NPV of 33.3% in predicting obstetrical outcome. CPR value of ≤1 had highest sensitivity of 66.67%, specificity of 83.33% in predicting abnormal neonatal outcome. Mohamed ML et al., claimed that C/U of less than 1.1 was the best predictor of adverse perinatal outcome [12]. However, Ciobanu A et al., have stated that MCA-PI and CPR increased with gestational age starting from 20 weeks' gestation to reach a peak at around 32 and 34 weeks, respectively, and thereafter decreased, whereas UA-PI decreased linearly with gestational age from 20 to 42 weeks. Thus, according to them, compared to the general population, significant deviations in multiples of the median values of UA-PI, MCA-PI and CPR were observed in subgroups of maternal age, body mass index, racial origin, method of conception and parity [13].

Ropacka-Lesiak M et al., concluded that the CPR shows the highest sensitivity in prediction of FHR abnormalities and adverse neonatal outcome in uncomplicated pregnancies at 40 weeks and beyond. Thus, CPR is useful in antenatal monitoring of these women in order to select those at high-risk of intra- and postpartum complications [1]. However, the present study showed lower sensitivity of CPR in predicting abnormal outcome. This can be attributed to smaller sample size. Hence, there is a need for study to be conducted on larger samples to determine the real effect of CPR in predicting abnormal obstetric and neonatal outcome.

		CPR							
		Abnormal				Normal			
		Present study	Ropacka-Lesiak M et al., [1]	Dall'Asta A et al., [10]	Gruttner B et al., [11]	Present study	Ropacka-Lesiak M et al., [1]	Dall'Asta A et al., [10]	Gruttner B et al., [11]
Foetal heart tracings	Non reassuring	45%	62.3%	-	-	30.00%	19%	-	-
Induction	Yes	80%	-			55.00%	-		
Mode of delivery	LSCS	30%	24.6%	24.1%	71.4%	25.00%	7.6%	20.3%	47.9%
	Instrument	15%	-	-	-	12.50%	-	-	-
Foetal distress	Yes	55%	-	-	-	22.50%	-	-	-
Liquor	Meconium	25%	46.4%	-	-	10.00%	24.1%	-	-
LBW	<2.5 kg/<10th percentile	15%	5.8%	11.1%		2.5%	0%	7.7%	-
NICU stay		5%	-	1.9%	-	2.50%	-	1.2%	-
Adverse neonatal outcome		20%	50.7%	33.3%	-	5%	6.3%	28%	-

[Table/Fig-13]: Comparison of obstetric outcome and neonatal outcome [1,10,11].

Limitation(s)

In this study doppler's assessment were not blinded, giving rise to possibility that this knowledge could have influenced subsequent clinical intervention and treatment effect. Another limitation could be non inclusion of cord blood analysis as a part of adverse neonatal outcome.

CONCLUSION(S)

There was significant association between foetal distress and abnormal CPR. In low-risk pregnancies with EFW >10th centile, abnormal CPR have significant association with adverse obstetric outcome, and these cases requires vigilant intrapartum monitoring. Therefore, even in those low-risk cases with EFW >10th centile, foetal dopplers helps in better management, including plan of delivery and intrapartum monitoring. So, routine measurements of foetal dopplers after 35 weeks of gestation in these cases, helps in better management.

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PARTICULARS OF CONTRIBUTORS:

1. Senior Resident, Department of Obstetrics and Gynaecology, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India.
2. Senior Consultant, Department of Obstetrics and Gynaecology, Bangalore Baptist Hospital, Bangalore, Karnataka, India.
3. Senior Consultant, Department of Obstetrics and Gynaecology, Bangalore Baptist Hospital, Bangalore, Karnataka, India.
4. Head, Department of Obstetrics and Gynaecology, Bangalore Baptist Hospital, Bangalore, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. C Kavyarani,
#28, Beereshwara, 4th Cross, Jayanagar, Kolar-563101, Karnataka, India.
E-mail: kavyaranic@gmail.com

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