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A correlation study of arterial stiffness with P300 event-related potential in non-haemodialytic and haemodialytic chronic kidney disease patients of renal origin

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is associated with hypertension. The renal micro-vessels are vulnerable to the pulsatile nature of systemic pressure leading to arterial stiffness, which may lead to progressive renal disease besides other mechanisms. The stiffened cerebral vasculatures may also cause neural injury. Thus, cognitive impairment is prevalent in CKD patients. However, very few studies have attempted to examine the association of arterial stiffness with P300 event-related potential (P3ERP) in CKD patients of primary renal disease in the Indian population, which forms the basis of the study.

Materials and Methods: Twenty-three age- and sex-matched non-haemodialytic and haemodialytic CKD patients were recruited in this cross-sectional and observational study. Montreal cognitive assessment questionnaire was applied to them to estimate global cognitive level. Peripheral and central blood pressure, augmentation index, brachial-ankle pulse wave velocity (baPWV), heart rate and P300 ERP were recorded. Biochemical analysis of the serum was also done. Appropriate statistical tests were performed to compare the differences between the variables of the two groups. Spearman's Correlation test was performed to examine the relationship between vascular parameters and P300 ERP metrics.

Results: Haemodialytic CKD patients exhibit early vascular ageing than non-haemodialytic CKD patients as evidenced by increased heart rate (P = 0.001) and higher central diastolic (P = 0.035) and peripheral diastolic blood pressure (P = 0.042). Although there was no significant difference in latency and amplitude of P300 ERP between the two groups, a significant positive association between baPWV and amplitude of P300 ERP was found. Moreover, higher serum phosphate (P = 0.021) and uric acid levels (P = 0.017) in haemodialytic patients promote vascular stiffening.

Conclusion: It may be concluded that early vascular ageing in CKD patients occurs due to the interplay of multiple physiological factors, which finally perturb cerebral haemodynamics and are responsible for the cognitive impairment observed in these patients.

Keywords: Arterial stiffness, Blood pressure, Event-related potential, Chronic kidney disease, Vascular ageing

INTRODUCTION

Chronic kidney disease (CKD) is known to be associated with hypertension. The pathophysiology of hypertension in CKD is quite complex and involves multiple factors such as the decrease in nephron mass, increased retention of sodium thereby causing an increase

in extracellular fluid volume, sympathetic system over-activity, activation of hormones with special reference to Renin-Angiotensin-Aldosterone System and endothelial dysfunction.[1] The renal micro-vessels are particularly vulnerable to the pulsatile nature of systemic pressure, which may lead to arterial stiffness. Increased central pulse pressure (PP) and pulse wave reflection due to arterial stiffness play a pivotal role in the progression of renal injury. Besides this, other mechanisms such as inflammation, uraemia, anaemia and oxidative stress are also involved in renal injury and microvascular damage.

The cerebral micro-vessels in CKD patients may also be perturbed because of changes in systemic circulation, which may lead to various cerebral pathologies such as cognitive impairment and stroke. Cognitive impairment is documented to be prevalent in 10–40% of CKD patients. Moderate-to-severe degree of cognitive impairment is prevalent in 70% of haemodialytic CKD patients.[2] Therefore, it is tempting to state that impaired vascular function in CKD patients may be linked to the development of their cognitive impairment due to cerebral microvascular involvement. Several studies have attempted in the past to determine cognitive impairment in CKD patients with the help of neuropsychological tests utilising various questionnaires such as mini-mental state examination and California verbal learning test. Few studies have assessed event-related potentials (ERP) such as P300 or P3 to evaluate cognitive function in CKD patients and haemodialytic patients.[3,4] The latency of P3 denotes the rapidity of information processing, the attention-based difference in amplitude and the novelty of the stimulus.[5] However, very few studies have attempted to examine the association of arterial stiffness (utilising various physiological surrogate markers such as brachial-ankle pulse wave velocity [baPWV], augmentation index [AIx]) with cognitive function evaluating P300 ERP (P3ERP) in CKD non-haemodialytic and haemodialytic patients of primary renal disease in Indian population, which forms the basis of the study.

MATERIALS AND METHODS

The present study was conducted after obtaining approval by the Institutional Ethics Committee, All India Institute of Medical Sciences (AIIMS) Bhubaneswar (IEC/AIIMS BBSR/PG thesis/2021–22/05). The study was a cross-sectional and observational one. The study participants were 18–50 years of both genders non-haemodialytic and haemodialytic CKD patients of primary renal disease with normal auditory capability. The patients with h/o diabetic nephropathy, congenital renal anomaly, autoimmune and endocrine diseases affecting blood vessels, peripheral vascular disease, any psychiatric illness and substance use disorder were excluded from the study. The non-haemodialysis CKD patients from the outpatient department of nephrology and haemodialysis CKD patients from the dialysis unit of the department of nephrology were recruited for the study. The sample size was calculated as 12 in each group, considering power as 90%, level of significance as 0.05 and 10% as a dropout. Finally, 23 subjects were recruited in two groups namely, group 1 (non-haemodialytic CKD patients) and group 2 (haemodialytic CKD patients). The participants were requested to report at the Clinical Physiology Laboratory for recording of physiological parameters. They were asked to refrain from physical exertion, drinking beverages and smoking 2–3 h before the test. The written informed consent was obtained from them before taking relevant demographic profiles, anthropometric measurements and recording of the physiological parameters. The protocol of the present study is shown in Figure 1.

The Montreal Cognitive Assessment (MOCA) questionnaire was applied to the participants to estimate the global cognitive level. A sum of the total score of 26 or more was considered normal. Brachial blood pressure was measured by a digital oscillometer following standard protocol. Mean arterial pressure and PP were derived from the data obtained. Resting central blood pressure (CBP), AIx and pulse rate were recorded with the help of a Central Blood Pressure Recording Instrument (USCOM make BP + [cardioscope II], Australia).

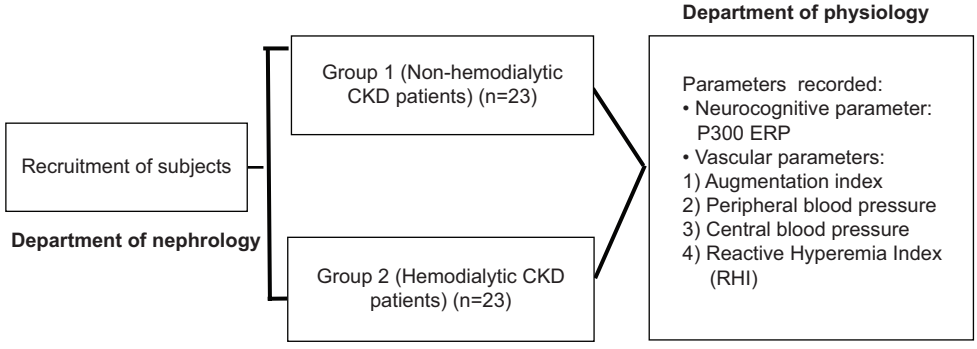

Figure 1: The protocol of the present study. CKD: Chronic kidney disease, ERP: Event-related potential

Recording of baPWV

The subject took rest for 5 min in the supine position. Then, pulse waveforms of brachial and posterior tibial arteries were recorded simultaneously by pulse transducers for 5 min using Powerlab™ 4/35 hardware (AD Instruments, Sydney, Australia). Labchart™ 8 reader software was used to analyse the data (AD Instruments, Sydney, Australia). The sample acquisition frequency was set at 1000 Hz. The components below 50 Hz were stored using a low pass filter, and the wavefront was determined. The time interval between the foot of the wavefront of brachial and ankle waveforms was designated as Pulse Transit Time. The distance between the sampling points of baPWV was calculated as follows: baPWV = (La-Lb)/ΔTba where Lb = (0.2195 × suprasternal notch to brachium [in cm] −2.0734) and La = (0.8129 × suprasternal notch to ankle [in cm] +12.328), La and Lb are distances and ΔTba is pulse transit time. For calculation of Lb, the superficial length from the suprasternal notch to the brachium, where the pulse transducer was placed, was noted, and for calculation of La, the superficial length from the suprasternal notch to the ankle, where the pulse transducer was placed, was noted.[6]

Recording of endothelial dysfunction

Both electrocardiogram (ECG) and pulse wave signals were acquired using Powerlab™ 4/35 hardware (AD Instruments, Sydney, Australia). The pulse transducer was fixed on the middle finger of the right hand. A sphygmomanometer cuff was applied to the right forearm to produce arterial occlusion. Standard bipolar limb lead II ECG was recorded simultaneously. Baseline ECG and pulse wave signals were recorded for 5 min. Arterial occlusion was produced by raising cuff pressure to 50 mm Hg above baseline systolic blood pressure and was maintained for 3 min. After deflating the cuff, the finger pulse wave amplitude was recorded for another 5 min. The data were analysed offline to determine the reactive hyperaemia index (RHI), which was calculated as the ratio of post-occlusion amplitude to baseline amplitude of the arterial pulse wave.[7]

Recording of P300

The subject took a rest for 5 min in the sitting position. The electrodes were placed on A1, A2 (reference electrodes), FPz (grounding electrode), Fz, Cz and Pz (active electrodes) positions after proper cleaning and abrasion of the areas of the scalp as per the International 10–20 system. All the electrodes were connected to the acquisition instrument through a jack box (Neuropack MEB 2300 K [Nihon Kohden, Japan]). The impedances of all electrodes were kept below 5 kΩ. The auditory stimuli were presented through headphones in the 'oddball paradigm' at the rate of 0.5 Hz. The subject responded to target auditory stimulus (40 dB at 2 kHz tone, 20% rare) in the background of non-target auditory stimuli (40 dB at 1 kHz tone, 80% frequent). A positive potential latency of approximately 300 ms was recorded after the target stimulus, that is P300. The experiment was conducted in two blocks, each comprising 30 trials.

Biochemical analysis of the blood

Biochemical analysis of the serum for estimation of serum urea, creatinine, uric acid, sodium, potassium, calcium, phosphate, PTH and alkaline phosphate was carried out in the central biochemical laboratory as prescribed by the Nephrologist. Haemoglobin estimation was also done to assess the anaemic status of the patient.

Statistical analysis

The normality of the data was assessed using the Shapiro-Wilk test. The non-normally distributed data are presented as median with interquartile range, and normally distributed data are presented as mean ± standard deviation. Mann–Whitney U-test was performed to compare the difference between non-normally distributed variables of the two groups, and the unpaired *t*-test was performed to compare the difference between normally distributed variables of the two groups. Spearman's Correlation test was performed to examine the relationship between vascular parameters and P300 ERP metrics. The data tabulation and basic calculations were done using a computer program (Microsoft Excel 2019, Microsoft Corp., Redmond, WA), and statistical analysis was done by the Statistical Package for the Social Sciences (SPSS) version 26 (SPSS Inc., Chicago, II, USA). A two-sided $P < 0.05$ was taken as the cutoff level of significance.

RESULTS

In the present study, 23 study participants were recruited in each group. In group 1, 17 study participants were men, and six were women, and in the haemodialytic group, 21 study participants were men and two were women. The anthropometric, clinical and biochemical data of the study participants are shown in Table 1.

It is evident from Table 1 that the study participants of the group 1 are older than those in the group 2 ($P = 0.025$). BMI is significantly more in group 1 than in group 2 ($P = 0.008$). The estimated glomerular filtration rate (eGFR) is significantly more in group 1 than in group 2 ($P = 0.000$). Among the biochemical parameters, serum urea ($P = 0.010$), creatinine ($P = 0.000$), potassium ($P = 0.000$), phosphate ($P = 0.021$) and parathyroid hormone (PTH) ($P = 0.000$) were significantly more in group 1 than group 2. However, serum-ionised calcium ($P = 0.000$) and uric acid ($P = 0.017$) were significantly higher in group 1 than in group 2.

Table 1: Anthropometric and clinical, biochemical data of the study participants.

Parameters	Group 1 (*n*=23)		Group 2 (*n*=23)		*P*-value
	Median	IQR	Median	IQR	
Age (years)	42.00*	37.00–46.00	32.00	24.00–42.00	0.025
Weight (kg)	49.00	45.00–58.00	49.00	41.40–51.70	0.206
BMI (kg/m2)	19.60**	18.70–21.80	17.10	15.80–19.60	0.008
eGFR (mL/min/1.73 m^2)	18.20***	10.00–26.00	8.00	6.00–9.00	0.000
Serum urea (mg/dL)	79.00	48.00–115.00	106.00**	88.00–139.00	0.010
Serum creatinine (mg/dL)	4.20	2.30–5.90	9.00***	7.88–10.96	0.000
Serum sodium (mEq/L)	137.00	133.00–138.00	137.00	134.00–138.00	0.674
Ionised calcium (mmol/L)	1.15***	1.08–1.24	0.93	0.87–1.01	0.000
Serum PTH (ng/L)	189.20	116.90–226.40	365.00***	282.20–562.80	0.000
Serum ALP (U/L)	103.00	87.00–140.00	98.00	72.00–172.00	0.553
	Mean±SD		Mean±SD		
Height (cm)	159.96±8.67		164.26±7.86		0.085
Serum uric acid (mg/dL)	6.58±1.82		8.03±2.15*		0.017
Serum potassium (mEq/L)	4.45±0.84		5.39±0.66***		0.000
Serum phosphate (mg/dL)	4.13±0.90		5.02±1.54*		0.021
Serum haemoglobin (g/dL)	10.01±2.09		9.72±1.57		0.595

*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$; IQR: Inter-quartile range, SD: Standard deviation, BMI: Body mass index, eGFR: Estimated glomerular filtration rate, PTH: Parathyroid hormone, ALP: Alkaline phosphatase

The vascular parameters of the study participants of the two groups are presented in Table 2. Among the vascular parameters, the heart rate was significantly higher in group 1 than in group 2 ($P = 0.001$). Both peripheral ($P = 0.042$) and central diastolic blood pressure ($P = 0.035$) of group 2 were found to be significantly higher than group 1.

The metrics of P300 ERP recorded at Fz, Cz and Pz electrode positions were compared between the groups. The data are presented in Table 3. MOCA score was assessed for 15 study participants of group 1 and 16 study participants of group 2. No significant difference in MOCA scores was found between the two groups ($P = 0.264$). It is evident from Table 3 that there is no significant difference in amplitude and latency of P300 ERP as recorded from Fz, Cz and Pz electrode positions between the two groups.

Spearman correlation test was performed to examine the relationship of vascular parameters with the metrics of P300 ERP. Significant positive correlation between baPWV and Fz P300 amplitude ($P = 0.033$, r = 0.316), baPWV and Cz P300 amplitude ($P = 0.024$, r = 0.334), as well as baPWV and Pz P300 amplitude (P = 0.011, r = 0.373), were found. However, no significant correlation between metrics of P300 ERP and RHI, Central systolic blood pressure (CSBP), Central diastolic blood pressure (CDBP), AIx and resting heart rate was found.

DISCUSSION

In the present study, among the vascular parameters, CDBP and PDBP were significantly higher in group 2 than in group 1. CKD is characterised by a reduction in renal autoregulation, an increase in the direct transmission of systemic blood pressure to glomeruli, and an increase in proteinuria. Thus, any increase in CBP hastens the progression of CKD. Conversely, a lower CBP is associated with a better cardiovascular outcome.[8] Studies have shown that central aortic pressure is more accurate in predicting target organ damage.[9,10] Therefore, during haemodialysis, monitoring of both central and peripheral blood pressure will help determine the target organ perfusion. The present study corroborates this statement.

RHI is a non-invasive method for evaluating endothelial dysfunction and a dependable biomarker for major cardiovascular and cerebrovascular events, and mortality.[11] During reactive hyperaemia, NO released from the endothelial cells relaxes vascular smooth muscle, reducing vascular tone.[12] In the present study, no significant difference in RHI was observed between the two groups. Previously, it has been documented that RHI did not decline with decreasing renal function.[13] The findings of the present study are in consonance with this report. Further research is required to determine whether RHI could predict cardiovascular outcomes in CKD patients.

The baPWV indicates the properties of both the medium-sized and the lower limb arteries and is an important non-invasive surrogate marker for measuring arterial stiffness. In comparison to cfPWV (carotid-femoral Pulse Wave Velocity), measuring baPWV requires less time and is less stressful for subjects.[14] In the present study, no significant difference in

Table 2: Vascular parameters of the study participants by group.

Vascular parameters	Group 1 (*n*=23)		Group 2 (*n*=23)		*P*-value
	Median	(IQR)	Median	IQR	
Heart rate (Beats per min)	72.00	62.00–78.00	83.00***	75.00–104.00	0.001
PSBP (mmHg)	132.00	117.00–147.00	142.00	124.00–165.00	0.206
AIx (%)	100.00	53.00–127.00	93.00	44.00–113.00	0.356
baPWV (cm/s)	1040.72	921.89–1270.24	1250.17	944.90–1796.33	0.116
Peripheral pulse pressure (mmHg)	47.00	44.00–54.00	46.00	39.00–53.00	0.385
Central pulse pressure (mmHg)	39.00	36.00–48.00	36.00	28.00–45.00	0.108
	Mean±SD		Mean±SD		
PDBP (mmHg)	83.87±16.53		95.43±20.71*		0.042
CSBP (mmHg)	127.43±24.73		135.09±28.38		0.335
CDBP (mmHg)	85.74±16.671		97.87±20.85*		0.035
Reactive hyperaemia index	1.00±0.33		1.06±0.34		0.589
Peripheral mean arterial pressure (mmHg)	100.90±18.16		111.58±22.60		0.084
Central mean arterial pressure (mmHg)	99.64±18.84		110.28±22.80		0.091

*$P \leq 0.05$, ***$P \leq 0.001$; IQR: Inter-quartile range, SD: Standard deviation, AIx: Augmentation index, baPWV: brachial-ankle pulse wave velocity, PDBP: Peripheral diastolic blood pressure, CSBP: Central systolic blood pressure, CDBP: Central diastolic blood pressure

Table 3: Neurocognitive parameters: P300 event-related potential recorded at various electrode positions from the study participants and MOCA score by group.

Parameters	Group 1 (*n*=23)		Group 2 (*n*=23)		*P*-value
	Median	(IQR)	Median	IQR	
Fz P300 latency (ms)	368.00	351.00–433.00	362.00	351.00–415.00	0.742
Cz P300 latency (ms)	368.00	344.00–416.00	359.00	339.00–394.00	0.758
Pz P300 latency (ms)	375.00	343.00–428.00	366.00	353.00–403.00	0.758
Cz P300 amplitude (μV)	10.01	5.31–14.57	10.33	6.69–17.31	0.374
MOCA (score out of 30)	22.00	20.00–24.00	23.00	21.00–26.00	0.264
	Mean±SD		Mean±SD		
Fz P300 amplitude (μV)	11.04±5.63		13.83±7.46		0.160
Pz P300 amplitude (μV)	9.82±5.88		13.20±6.65		0.075

IQR: Inter-quartile range, SD: Standard deviation, MOCA: Montreal cognitive assessment, Fz:Frontal midline, Cz: Central midline, Pz: Parietal midline

baPWV between the two groups was observed, though the median value of baPWV is more than 1000 cm/s in both groups. This indicates enhanced arterial stiffness of the study participants in both groups when compared to the age-matched normal healthy subjects.[15] However, a prospective, longitudinal study conducted on CKD patients of stages 3–5 (n = 186) documented that the group with the highest baPWV was associated with rapid progression in CKD.[16] AIx is the ratio between central augmented pressure and central PP. It quantifies the contribution of wave reflection to the formation of the central pressure waveform. A previous study reported that non-haemodialytic CKD patients with an increased AIx have a higher risk of deteriorating renal function.[17] However, no significant difference in AIx between the two groups was observed in this study.

In the present study, the resting heart rate of group 2 was significantly higher than group 1. Increased resting heart rate indicates impaired vagal tone, and enhanced sympathetic activity, which was documented previously by a prevalence study conducted on a cohort of 2535 clinically stable haemodialytic patients as well as a prospective study conducted on 32 patients undergoing long-term haemodialysis.[18,19]

The latency and amplitude of P300 ERP are considered significant correlates of cortical function.[20] Complex or multiple tasks cause a reduction in P300 amplitude and lengthen peak latency. The present study did not find any statistically significant difference in amplitude and latencies of P300 ERP between the two groups. A prospective study reported that the amplitudes of P300 ERP were similar among haemodialytic, ambulatory peritoneal dialytic and healthy control groups.[21] The present study corroborates the result of this previous study. However, another study documented an incremental trend in P300 latencies as the severity of CKD increases,[3] which was not found in the present study.

In the present study, a significant positive correlation between baPWV and Fz P300 amplitude, baPWV and Cz P300 amplitude and baPWV and Pz P300 amplitude was found, though no statistically significant correlations were found between baPWV and latencies of P300 ERP. The developmental trajectories of the parietal P300 reach their peak around 21 years and then decrease gradually, while the frontal P300 reaches its peak around 46 years and shows a less pronounced decrease in amplitude with increasing age, according to the compensation-related utilisation of neural circuits hypothesis.[22] The significant association between baPWV and amplitude of P300 ERP recorded at Fz, Cz and Pz positions signifies that as arterial stiffness increases, it may perturb cerebral haemodynamics, which may affect the structural entity of the brain. This leads to more allocation of attentional resources to an alternating neural network or utilises existing neural networks differently during task discrimination for the completion of a given cognitive task, as put forward by a previous study as well.[23]

The MOCA is a 10-min, one-page, 30-point test that assesses various cognitive domains and it is easy to apply to accurately differentiate between mild cognitive impairment and healthy control.[24] In the present study, no significant difference in MOCA score was observed between the two groups. However, a significant decline in global cognitive scores in the haemodialytic group was reported by a previous study.[25] The discrepancy in the result may be due to the non-inclusion of the healthy control group in the present study.

CKD is a chronic, low-grade inflammatory condition that causes alteration of endothelial function and vessel wall thickening. It also favours calcium deposition in the arterial wall.[26] All these biological events lead to loss of arterial compliance and give rise to 'early vascular ageing' (EVA).[27,28] An increase in serum phosphate enhances the phenomenon of EVA by promoting vascular calcification. Hyperphosphatemia, a late finding in CKD, induces phenotypic conversion of vascular smooth muscle cells to osteochondrogenic type. Moreover, it exerts changes in the extracellular milieu of vascular smooth muscle cells. Altogether, these changes favour vascular calcification and stiffening.[29] CKD is also characterised by an increase in serum uric acid level, which reduces endothelial nitric oxide synthase activity causing a decrease in NO production and VSMC proliferation.[30,31] In the present study, serum phosphate, uric acid, urea and creatinine levels in group 2 are significantly higher than in group 1. These uremic toxins, which can serve as vascular toxins, are more pronounced in the haemodialytic group. The serum ionised calcium level is significantly less in group 2 than in group 1, which indicates a lesser amount of calcium absorption from the gastrointestinal tract. It may happen due to decreased synthesis of 1, 25-dihydroxy cholecalciferol (vitamin D3) by the diseased kidney. In turn, the decreased level of serum calcium stimulates parathormone secretion. It is evident that the altered biochemical and physiological changes in CKD may bring about vascular stiffness and microvascular changes in target organs such as the brain, which eventually leads to cognitive dysfunction. It can also be argued that systemic arterial stiffness plays a pivotal role in inflicting kidney injury, and this becomes a vicious circle, which finally affects the perfusion pressure to target organs such as the brain.

The present study has several limitations that warrant discussion. The result of the present study cannot be generalised due to the small sample size. A healthy control group could not be included in the present study, which could act as a comparator for the two study groups.

It may be concluded from the present study that haemodialytic CKD patients exhibit early vascular ageing in comparison to age- and sex-matched non-haemodialytic CKD patients due to their enhanced sympathetic activity as evidenced by their increased heart rate and higher central and peripheral diastolic blood pressure. Although there was no significant difference in latency and amplitude of P300 ERP between the two groups, a significant positive association between baPWV and amplitude of P300 ERP was found. It indicates that the perturbed cerebral microvasculature might affect cognitive function in those patients. Moreover, higher serum phosphate and uric acid levels in haemodialytic patients promote vascular stiffening.

CONCLUSION

It may be concluded from the present study that early vascular ageing is evidently more in hemodialytic CKD patients in comparison to age and sex-matched non-hemodialytic CKD patients because of the interplay of myriad physiological factors, which finally perturb cerebral haemodynamics and that may lead to the cognitive impairment observed in these patients.

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Authors' contributions

APR: Data acquisition, data analysis and interpretation, manuscript writing and editing; MK: Concept designing, data analysis and interpretation, manuscript writing and editing; BK: Data acquisition, data analysis and manuscript editing; SKP: Recruitment of the study participants, data interpretation and manuscript editing; PN: Concept designing, data interpretation and manuscript editing.

Data availability statement: The data set is shown in the tables of the manuscript.
Ethical approval: This study protocol was reviewed and approved by the Institute Ethics Committee, AIIMS Bhubaneswar, IEC/ AIIMS BBSR/PG thesis/2021–22/05.
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