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C-reactive protein levels among hypertensive patients attending University of Nigeria Teaching Hospital Ituku-ozalla, Enugu State, Nigeria

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Abstract

The blood level of C-reactive protein (CRP) has been postulated to increase in hypertensive patients but has not been implicated as a risk factor for high blood pressure. This prompted this study to investigate the level of CRP of hypertensive patients at the University of Nigeria Teaching Hospital, Ituku-Ozalla, and Enugu state. Eighty-nine subjects of which 50 were hypertensive patients (test subjects) and 39 apparently healthy individuals (control subjects) volunteered in the study. A structured questionnaire was used to capture the bio-data and other vital information from the participants of which virtually all the test subjects were on anti-hypertensive drugs. Anthropometric measurements were taken, blood samples were collected and CRP was analyzed using the Enzyme-Linked Immunosorbent Assay method. Data were analyzed using the student's test and Analysis of Variance (ANOVA). There was no significant statistical difference (P>0.05) in CRP levels (µg/ml) in all the comparisons; that is between all male and female study populations (401-478 and 3.61-4.24), between tests and controls (3.62-3.85 and 4.06-526), between male tests and male controls (3.76-3.55 and 4.24-5.80), between female tests and female control (3.62 ±3.85 and 3.76-3.55) between male tests and female tests (3.50-414 and 381-4.531, and between male controls and female controls (4.24 ±5.80 and 3.81-4.55). It was also observed that there was no relationship between the duration of hypertension with the CRP levels in the test subjects. These results suggest that the C-reactive protein levels may be increased in hypertensive patients but may be decreased by antihypertensive therapies. More studies are needed and these findings warrant further evaluation in randomized trials. A longitudinal study to fully assess the effect of antihypertensive drugs on the level of C-reactive protein in hypertensive patients may also be of great essence.

Keywords: C - reactive protein; Hypertension; Blood Pressure; Antihypertensive Drugs; Hypertensive Patients

1. Introduction

In general, cardiovascular diseases (CVD) have been shown to be responsible for 30% of worldwide mortality, and high blood pressure (HBP) alone contributes to 7.6 million premature deaths each year [1]. HBP represents one of the commonest chronic health problems and is an important modifiable risk for vascular events, and mortality in the world.

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High blood pressure - also known as raised blood pressure or hypertension is a condition in which the blood circulates at a persistently increased pressure [2].

Hypertension is a well-known disease that is associated with the cardiovascular system of humans. It has been considered one of the major risk factors influencing the development of cardiac and cerebrovascular diseases, thus playing an important role in the development of atherosclerosis, as well as modifying the geometry of the left ventricle which results in an increase in the thickness of the cardiac wall and mass. Authors estimate that from 1975 to 2015, the number of adults with this problem have increased from 594 million to more than 1.11 billion [3]. In addition, many hypertensive patients are not diagnosed for years and those diagnosed most times, are wrongly diagnosed, and thus, are inappropriately treated for decades.

It is a well-established fact that; C-reactive protein (CRP) is an acute-phase protein and it is a major diagnostic factor that is indicative of recent or any early inflammation. This protein is produced in the liver and is usually found at concentrations of less than 10 mg/L in the bloodstream in the presence of an infectious/ inflammatory disease state. CRP levels tend to rise rapidly within the first 6 to 8 hours and peak at levels of up to 350-400 mg/L after 48 hours [2]. It has been observed that once an inflammation or tissue destruction is resolved, CRP levels tend to fall, thus making it a useful marker for disease activity monitoring.

There is a large body of evidence indicating that inflammation plays a crucial role in all steps characterizing the atherosclerotic process [4]. C reactive protein (CRP) is a circulating marker of inflammation that recently emerged as a powerful independent determinant of cardiovascular events [5]. It has been observed that hypertension is closely linked to inflammation. CRP concentration in the body is of importance because reports have shown that there is a strong connection between its level and the major indicator of hypertension – High blood pressure [5].

Circulating levels of CRP are clinically used to predict the occurrence of cardiovascular events and to aid in the selection of therapies based on more accurate risk assessment in individuals who are at intermediate risk [5]. Reports have shown that; there is a possibility of reduction in CRP levels when anti-hypertensive drugs are used and it does this in such a way that, it will have negligible effects on the blood pressure readings of the patient [4]. CRP in individuals with normal blood pressure, at baseline, can help predict or give an early indication of the development of hypertension. [5] This could possibly make CRP a likely very invaluable tool for the assessment of prehypertension.

Recent awareness of the utility of measuring CRP as a risk factor for cardiovascular disease has led to the development of high-sensitivity CRP (hs-CRP) [5]. Mild elevations in CRP concentration predict myocardial infarction, stroke, and vascular death in a variety of clinical settings, including hypertension. For hypertensive patients, therefore, measurements of this marker may help in instituting measures to prevent these complications, and also in the evaluation of the severity of the disease, efficacy of the treatment, and prognosis [1]. Despite these overwhelming facts, there is a dearth of literature on CRP levels and its clinical utility on hypertensive subjects in our setting (South-East Nigeria), hence the need for this study.

Therefore, with this study, we aim to determine the C-reactive protein levels in hypertensive patients in the University of Nigeria Teaching Hospital, Ituku-Ozalla, in Enugu state and compare them with those of non-hypertensive subjects. In addition, we aim to also evaluate the effects of duration of hypertension on CRP levels.

2. Material and methods

2.1. Study Area

The prospective study was carried out at the University of Nigeria Teaching Hospital (U.N.T.H.), Ituku-Ozalla, Enugu, South-East Nigeria. This hospital serves as a research hub for South East. It is located along Enugu – Port Harcourt Express Way, 21 kilometers from Enugu capital city. It covers an area of 200 acres of land.

2.2. Ethical Considerations and Informed Consents

Ethical clearance was duly obtained from the ethical committee of the University of Nigeria Teaching Hospital, Ituku/Ozalla, and Enugu. Informed consent was also duly obtained from the participants and absolute confidentiality was maintained. A structured questionnaire was used to get necessary data about the participants.

2.3. Study Population and Design

2.3.1. Sample size

A standard statistical formula by Araoye [6] was used to determine the sample size as follows:

$$N = Za^2\ P\frac{(1-P)}{d2}$$

N = Sample size

Za = Significant level which is set at 95% confidence interval (1.96)

P = Proportion of target population estimated.

d = Margin of error tolerated (5% i.e. 0.05)

Therefore, using 0.05 as proportion (derived from previous study) and 0.05 as absolute error, the sample size will be calculated as follows:

$$N\ = (1.96)^2 x\ 0.05\frac{(1\ -\ 0.05)}{(0.05)^2}$$

$$N\ =\ 3.8416\ x\ 0.05\frac{(0.095)}{0.0025}$$

$$N\ =\ 3.8416\ x\ 0.05\ x\ 380$$

$N = 72\ \pm 10\%$ attrition

$$N\ =\ 72.99\ \pm\ 7.299\ =\ 80.289$$

Therefore, the study population, therefore, targeted a minimum of 80 subjects.

2.3.2. Subjects

The study was carried out on a total number of 89 volunteers (50 test group and 39 control group) from UNTH and Enugu metropolis between the age of 18 years and above. Informed consent was obtained from each participant. Questionnaires were distributed and duly filled by the participants with the assistance of the researchers.

2.3.3. Selection of The Study Group

The test group comprised patients in the cardiology unit (Medical Out-Patients, MOP), the University of Nigeria Teaching Hospital, Itiku-Ozalla, who have been diagnosed with high blood pressure without a history of diabetes mellitus. Subjects that met these inclusion criteria were shortlisted and participants were selected by simple random sampling.

2.3.4. Selection of Control Group

The control group comprises 39 apparently healthy individuals with no history of high blood pressure, who freely wanted to participate in this study. The individuals that met the inclusion criteria were shortlisted and participants were selected by simple random sampling.

Inclusion and Exclusion Criteria

Inclusion criteria include

- For hypertensive patients
  - Recent confirmation of raised blood pressure
  - Exposure to hypertension for at least six months.

- For non-hypertensive patients.
  - Must not have had any history of high blood pressure

Exclusion criteria include being
- A smoker.
- An alcoholic.
- On hypertensive drug.
- Pregnant.

2.4. Sampling Technique

2.4.1. Anthropometric Measurements

The following anthropometric data were measured: height, weight, and blood pressure. Standing height was measured to the nearest centimeter (cm) using a stadiometer, footwear was removed. Weight was measured to the nearest kilogram (kg) with a manual Seca 761 scale (Vogel & Halke, Hamburg, Germany) after participants have removed outer garments, cell phones, and footwear. Body mass index (BMI) was calculated by weight in kilograms divided by height in meter square. Blood pressure (BP) and pulse rate were measured with an automated sphygmomanometer (OMRON HEM705CP, Omron Matsusaka Co. Matsusaka city, Mie-Ken, Japan) using appropriate cuff size after participants have sat undisturbed for at least 5 minutes. Three consecutive readings were taken one minute apart, and the mean of the three readings was used for the analysis.

2.5. Blood Collection and Handling

The blood sample was collected from the volunteers by venipuncture using a sterile 5ml needle and syringe. 2mls of blood were collected from a peripheral vein on the arm of each subject and immediately transferred into a plain tube. A plain tube sample was allowed to clot followed by clot retraction. The sample was centrifuged at 5000RPM for 5 minutes and the serum was dispensed into a serum container.

2.6. Laboratory Analysis

2.6.1. C - reactive protein Estimation

Method

C-reactive protein was analyzed using Enzyme-Linked Immunosorbent Assay (ELISA) method as reported by Kimberly et al. [7]

Principle of Method

The essential reagents required in immune-enzymometric assay include high affinity and specificity antibodies (enzyme and immobilized), with different and distinct epitope recognition, in excess, and native antigen. In this procedure, the immobilization takes place during the assay at the surface of a microplate well through the interaction of streptovidin coated on the well and exogenously added biotinylated monoclonal antibody. Upon mixing, the monoclonal biotinylated antibody, the enzyme-labeled antibody, and the serum containing the native antigen and the antibodies, without competition or static hindrance, form a sandwich complex.

2.7. Reagent Preparation: the reagents were prepared as follows:

- The serum diluent was diluted by adding up to 200mls in a suitable container with deionized water and was stored at 2-8°C for 48hours.
- The wash solution was diluted by adding 1ml of the solution to 49mls of distilled water (i.e. 1 in 50 dilutions).
- The working substrate was prepared by adding the contents of the amber vial labeled A to the clear vial labeled B. The yellow cap of the amber vial was used to cover the clear vial which contained the working solution.
- 1 in 200 dilutions of the serum was made by adding 10microlitre of the serum samples to 2mls of the serum diluent and was stored at 2-8°C.

Procedure

After the reagent preparation, the diluted sample which was stored at 2-8°C for 48hrs was run as follows:

- The microplates' wells were formatted for each serum reference, control and patient specimen to be assayed in duplicate
- 25microlitres of the appropriate serum reference, diluted control or specimen were pipetted into the various assigned wells.
- 100microlitres of CRP enzyme reagent was pipetted into each well and was swirled gently for 20-30secs.
- It was incubated for 15mins at room temperature, decanted gently and was blotted dry with absorbent paper.
- It was washed 3 times by adding 350microlitres of was wash buffer into each well, decanting and blotted dry.
- 100microlitres of the working substrate was added to each well and was incubated for 15mins without shaking at room temperature.
- The reaction was stopped with a stop solution and the absorbance was read at 450nm in a multi-plate reader.

2.8. Data Analysis

Data obtained from this study were analyzed using the statistical package for social sciences (SPSS) for Windows Inc. Chicago, IL, USA. Student's t-test was used to calculate differences between means, analysis of variance (ANOVA) was used to estimate differences between group means. All tests were two-tailed and p value <0.05 considered statistically significant.

3. Results

Legends: SysBP = Systolic Blood Pressure

DiaBP = Diastolic Blood Pressure

BMI = Body Mass Index

Table 1 The Mean ±SD of Age, SysBP, DiaBP, Pulse, Weight, Height, BMI and CRP of Males Vs Females

	All	Male	Female	P- value
	(n=89) Mean ±SD	(n=45) Mean ±SD	(n=44)Mean ±SD	
Age(yr)	50.81 ±14.73	48.76 ±14.98	15.91 ±14.33	0.185
SysBP(mm/Hg)	128.35 ±22.14	130.12 ±22.46	126.48 ±21.91	0.434
DiaBP(mm/Hg)	78.16 ±12.39	78.31 ±13.34	78.00 ±11.50	0.014
Pulse(BPM)	73.75 ±9.03	73.80 ±9.88	73.70 ±8.20	0.961
Weight(Kg)	79.25 ±14.68	77.49 ±14.24	81.06 ±15.07	0.256
Height (m)	1.67 ±0.09	1.71 ±0.08	1.63 ±0.08	0.000
BMI(Kg/m2)	28.47 ±5.37	26.39 ±4.44	30.59 ±5.45	0.000
CRP(microg/ml)	3.81 ±4.50	4.01 ±4.78	3.61 ±4.24	0.681

In table 1; it can be observed that DiaBP, Height, and BMI are statistically significant with P-value <0.05 when the male subjects were compared with female subjects.

Table 2 The Mean ±SD of Age, SysBP, DiaBP, Pulse, Weight, Height, BMI and CRP of Tests Vs Controls

	All	**Male**	**Female**	**P- value**
	(n=89) Mean ±SD	**(n=50) Mean ±SD**	**(n=39)Mean ±SD**	
Age(yr)	50.81 ±14.73	57.40 ±9.73	42.36 ±15.81	0.000
SysBP(mm/Hg)	128.35 ±22.14	139.96 ±22.14	113.46 ±9.93	0.000
DiaBP(mm/Hg)	78.16 ±12.39	82.68 ±13.69	72.36 ±7.25	0.000
Pulse(BPM)	73.75 ±9.03	74.66 ±9.16	72.59 ±8.85	0.286
Weight(Kg)	79.25 ±14.68	83.00 ±14.82	74.44 ±13.18	0.006
Height (m)	1.67 ±0.10	1.67 ±0.10	1.67 ±0.08	0.683
BMI(Kg/m2)	28.47 ±5.37	29.80 ±4.70	26.75 ±5.74	0.007
CRP(microg/ml)	3.81 ±4.50	3.62 ±3.85	4.06 ±5.26	0.645

In table 2; it can be observed that age, SysBP, DiaBP, weight and BMI, are statistically significant with P-value <0.05 when the test subjects were compared with control subjects.

Table 3 The Mean ±SD of Age, SysBP, DiaBP, Pulse, Weight, Height, BMI and CRP of Male Tests Vs Male Controls

	All	**Male**	**Female**	**P- value**
	(n=45) Mean ±SD	**(n=22) Mean ±SD**	**(n=23) Mean ±SD**	
Age(yr)	48.76 ±14.98	57.27 ±9.41	40.61 ±14.92	0.000
SysBP(mm/Hg)	130.12 ±22.46	148.18 ±17.88	112.96 ±8.35	0.000
DiaBP(mm/Hg)	78.31 ±13.34	86.77 ±12.95	70.21 ±7.46	0.000
Pulse(BPM)	73.80 ±9.88	72.72 ±10.92	74.83 ±8.90	0.482
Weight(Kg)	77.49 ±14.24	84.91 ±14.68	70.39 ±9.59	0.000
Height (m)	1.71 ±0.08	1.73 ±0.09	1.70 ±0.07	0.231
BMI(Kg/m2)	26.39 ±4.44	28.43 ±4.49	24.45 ±3.47	0.002
CRP(microg/ml)	4.01 ±4.78	3.76 ±3.55	4.24 ±5.80	0.742

In table 3; it can be observed that age, SysBP, DiaBP, weight and BMI were statistically significant with P-value <0.05 when the male test were compared with male control.

Table 4 The Mean ±SD of Age, SysBP, DiaBP, Pulse, Weight, Height, BMI and CRP of Female Test Vs Female Control

	All	Male	Female	P- value
	(n=44) Mean ±SD	(n=28) Mean ±SD	(n=16) Mean ±SD	
Age(yr)	52.91 ±14.33	57.50 ±10.15	44.88 ±17.18	0.004
SysBP(mm/Hg)	126.48 ±21.91	133.50 ±23.30	114.19 ±12.11	0.004
DiaBP(mm/Hg)	78.00 ±11.50	79.46 ±13.62	75.44 ±5.86	0.259
Pulse(BPM)	73.70 ±8.20	76.18 ±7.35	69.38 ±7.99	0.007
Weight(Kg)	81.06 ±15.07	81.50 ±15.03	80.25 ±15.61	0.795
Height (m)	1.63 ±0.08	1.62 ±0.07	1.64 ±0.09	0.350
BMI(Kg/m2)	30.59 ±5.45	30.89 ±4.65	30.07 ±6.77	0.638
CRP(microg/ml)	3.61 ±4.24	3.50 ±4.14	3.81 ±4.53	0.821

In table 4; it can be observed that age, SysBP and pulse were statistically significant with P-value <0.05 when the female test was compared with female control.

Table 5 The Mean ±SD of Age, SysBP, DiaBP, Pulse, Weight, Height, BMI and CRP of Male Tests Vs Female Tests

	All	Male	Female	P- value
	(n=50) Mean ±SD	(n=22) Mean ±SD	(n=28) Mean ±SD	
Age(yr)	57.40 ±9.73	57.27 ±9.41	57.50 ±10.15	0.936
SysBP(mm/Hg)	139.96 ±22.14	148.18 ±17.88	133.50 ±23.30	0.018
DiaBP(mm/Hg)	82.68 ±13.69	86.77 ±12.95	79.46 ±13.62	0.060
Pulse(BPM)	74.66 ±9.16	72.72 ±10.92	76.18 ±7.35	0.189
Weight(Kg)	83.00 ±14.82	84.91 ±14.68	81.50 ±15.03	0.425
Height (m)	1.67 ±0.10	1.73 ±0.09	1.62 ±0.07	0.000
BMI(Kg/m2)	29.80 ±4.70	28.43 ±4.49	30.89 ±4.65	0.066
CRP(microg/ml)	3.62 ±3.85	3.76 ±3.55	3.50 ±4.14	0.814

In table 5; it can be observed that SysBP, and height were statistically significant with P-value <0.05 when the male tests were compared with female tests.

Table 6 The Mean ±SD of Age, SysBP, DiaBP, Pulse, Weight, Height, BMI and CRP of Male Controls Vs Female Controls

	All	Male	Female	P- value
	(n=39) Mean ±SD	(n=23) Mean ±SD	(n=16) Mean ±SD	
Age(yr)	42.36 ±15.81	40.61 ±14.92	44.88 ±17.18	0.414
SysBP(mm/Hg)	113.46 ±9.93	112.96 ±8.35	114.19 ±12.11	0.709
DiaBP(mm/Hg)	72.36 ±7.25	70.21 ±7.46	75.44 ±5.86	0.025
Pulse(BPM)	72.59 ±8.85	74.83 ±8.90	69.38 ±7.99	0.057
Weight(Kg)	74.44 ±13.18	70.39 ±9.59	80.25 ±15.61	0.019
Height (m)	1.67 ±0.08	1.70 ±0.07	1.64 ±0.09	0.027
BMI(Kg/m2)	26.75 ±5.74	24.45 ±3.47	30.07 ±6.77	0.002
CRP(microg/ml)	4.06 ±5.26	4.24 ±5.80	3.81 ±4.53	0.804

In table 6; it can be observed that DiaBP, weight, height and BMI were statistically significant with P-value <0.05 when the male controls were compared with female tests

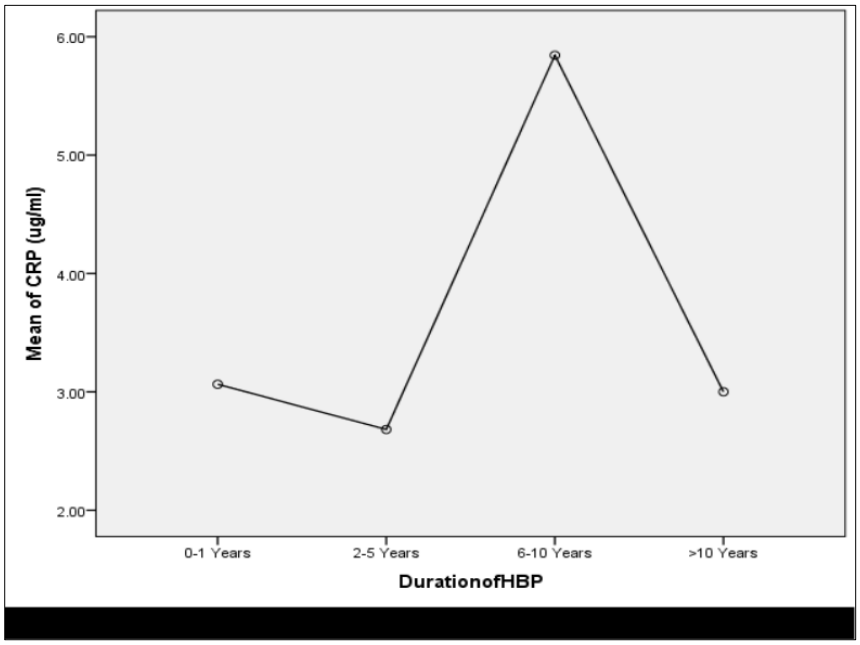

Figure 1 Mean of CRP Vs HBP Duration

4. Discussion

In this study, a comparison of results was made between male and female populations, tests and controls, male tests and male controls, female tests and female controls, male tests and female controls, and female tests and male controls. Our findings showed a significant difference between systolic pressure, diastolic pressure, and body mass index (BMI) between the test subjects and the control group. This is in line with the work done by Cappuccio et al., [8], which stated that there is a positive relationship between systolic blood pressure, diastolic blood pressure, and body mass index (BMI). An increase in BMI amongst the test subjects is due to an increase in body weight which could lead to the deposition of fats in the visceral organs, thus leading to atherosclerosis.

It was also observed that body mass index and blood pressure were statically significant between the male and female subjects. Regarding BMI, height is inversely associated with BMI in adults [9]. This relationship has been observed to be larger in women and has vastly increased with age. Nevertheless, in pre-pubertal children, there is a positive association between body mass index (BMI) and height (i.e. taller = higher BMI), while in adults, there is a negative association

between BMI and height, particularly in women [9]. In addition, during early life, greater maternal pregnancy weight gain, higher birth weight, and faster growth are associated with higher BMI [9].

This study revealed that there is no significant difference between the C - reactive protein level in test subjects and control subjects. This is in disagreement with the findings made by Smith et al., [10] and Hage [5] who proposed that the levels of C-reactive protein are higher in hypertensive patients. C-reactive protein is a plasma protein of the pentraxin family and an acute phase reactant that displays high sensitivity as a general inflammation marker. From the questionnaires answered by the test subjects, virtually all the test subjects were on hypertensive drugs during the study, thus lies the basis of our findings.

According to works by Fulop et al., [11] and Palmas et al., [12] on the effects of antihypertensive drugs on the level of C-reactive protein in patients diagnosed with hypertension, they suggested that antihypertensive drugs have a lowering effect or knock down the level of C-reactive protein in hypertensive patients. In the cases of hypertensive patients being treated with beta-blockers, it has been postulated that this group of drugs blocks the sympathetic nervous system which is responsible for the triggering of inflammatory responses, this, in turn, reduces the amount of c-reactive protein present in the serum [12]. It has also been reported that antihypertensive treatment with an angiotensin receptor blockers (ARB) ameliorated inflammatory processes and markedly reduced circulating pro-inflammatory mediators [13].

In addition, it was observed that there was no significant difference in the levels of C-reactive protein amongst the test subjects. This observation contradicts the findings of Dar et al., [14] which said that level of C-reactive protein is higher in hypertensive patients whose duration is ≤ 1 year than in those with longer duration. This controversy could be a result of the antihypertensive drugs being taken by the test subjects.

5. Conclusion

C-reactive protein (CRP), the prototypical acute phase reactant, is one of the most widely known biomarkers of cardiovascular disease. Data from this study revealed that C-reactive protein levels may be increased in hypertensive patients but may also be reduced drastically by antihypertensive drugs.

recommendation

However, the following recommendations may be of great essence:

- More studies are needed and these findings warrant further evaluation in randomized trials.
- A longitudinal study is needed to fully assess the effect of antihypertensive drugs on the level of C - reactive protein in hypertensive patients.
- Further studies should explore fresh subjects.

Compliance with ethical standards

Acknowledgments

Our profound gratitude goes to our Maker, who has found us fit, and worthy and brought this research to a successful end.

Disclosure of conflict of interest

We declare no conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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