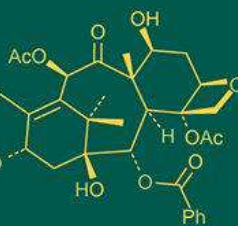
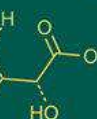
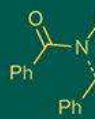
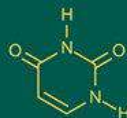
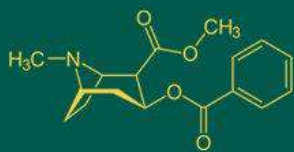


International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693
ISSN Online: 2617-4707
IJABR 2019; 3(2): 26-33
www.biochemjournal.com
Received: 16-05-2019
Accepted: 20-06-2019

Variation of serum beta-2 microglobulin in Senegalese chronic hemodialysis patients

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Abstract

Hemodialysis is an extrarenal purification technique widely used to increase life expectancy during chronic kidney disease. The latter contrasts with an impairment of quality of life due to joint complications caused by amyloidosis, resulting from the increase in the blood of beta-2 microglobulin (β_2m).

The objectives of our study were to determine the variation of serum β_2m in chronic hemodialysis patients monitored at the nephrology department hemodialysis unit of Aristide Le Dantec Hospital and to investigate possible correlations between serum β_2m and epidemiological parameters on the one hand and those of hemodialysis on the other. Serum β_2m was measured by a two-step sandwich immunoassay method with final fluorescence detection, using the VIDAS 3 (BIOMERIEUX) immunoassay automaton. The study population consisted of 35 patients, 57 % male and 43 % female, the mean age was 48.97 years. The average length of time on dialysis was 5.94 years. The initial nephropathy was nephroangiosclerosis in 40 % of cases. The vascular approach was by an arteriovenous fistula in 91.4 % and a temporary venous catheter in 8.6 %, only a synthetic membrane was used. Serum β_2m values were high with an average of 43.88 mg / l. Elevations in β_2m were correlated with sex ($p = 0.007$), age ($p = 0.007$), length of time on dialysis ($p = 0.0001$) and residual diuresis ($p = 0.035$). Therefore, it is important to include β_2m in the kidney disease monitoring report.

Keywords

Serum beta-2-microglobulin, chronic hemodialysis, Senegal

Introduction

Hemodialysis is a very common renal replacement technique. However, it is responsible for the accumulation of an amyloid substance mainly composed of β_2 -microglobulin (β_2m) [1]. The latter is believed to be responsible for osteoarticular symptoms including carpal tunnel syndrome and amyloid arthropathy in chronic dialysis patients [2, 3].

Moreover, β_2m is a key component of the adaptive immune system. It is a non-glycosylated polypeptide molecule of the major histocompatibility complex class I [4]. It circulates in the extracellular space and is filtered at the level of the kidneys by the glomeruli, then reabsorbed and catabolized at the tubular level. In case of renal dysfunction, this molecule cannot be eliminated by the kidneys. It is also described that the increase in β_2m can be influenced among other factors by the duration and type of dialysis membrane [5, 6].

To our knowledge, no study on β_2m is performed in dialysis patients in Senegal. The objectives of our study were to determine the variation of serum β_2m in chronic hemodialysis patients monitored at the nephrology department hemodialysis unit of Aristide Le Dantec Hospital and to investigate possible correlations between serum β_2m and epidemiological parameters on the one hand and those of hemodialysis on the other.

Material and Methods

This is a prospective, descriptive and analytical study, which is carried out over a period of 7 months from May to December 2017.

Study population

The study population consisted of chronic hemodialysis patients, monitored for at least 6 months at the nephrology department hemodialysis unit of Aristide Le Dantec. Patients receiving peritoneal dialysis, temporary hemodialysis due to complications of peritoneal dialysis, chronic renal failure patients dialyzed for less than 6 months and those with pathologies (B lymphoproliferative syndrome, viral infections ...) were not included in the study that can influence the values of serum β_2m . All the patients allied to the study gave their informed consent.

Determination of beta 2-microglobulin

The blood sample was taken from the arteriovenous fistula and the blood was collected in a dry tube. The samples were transported immediately, in an insulated bag, to the laboratory. After centrifugation, the serums were frozen at -20°C . The serum β_2m was measured by a two-step sandwich immunoassay method with a final fluorescence detection, using the VIDAS 3 immunoassay automaton (BIOMERIEUX).

Other parameters studied: urea, creatinine, calcium, phosphorus, parathormone (PTH), vitamin D and C - reactive protein (CRP).

Other data studied

The following data was collected in each patient's file:

- Epidemiological data: age, gender, pathological history, initial nephropathy
- Data related to hemodialysis: type of dialysis membrane, dialysis rhythm, vascular approach, age in dialysis, residual diuresis
- Clinical and paraclinical data: presence of joint pain, bone pain, presence of carpal tunnel syndrome, evolution.

Statistical analysis

The data has been entered with Sphinx software version 5.1.0.2. The analysis was carried out with the SPSS software (Statistical Package for Social Sciences) version 18. The descriptive study was carried out with the calculation of the frequencies and proportions for the qualitative variables and the calculation of the means and the standard deviation for quantitative variables. We compared the averages with the variance analysis test, and the Pearson correlation coefficient to determine the relationship between two continuous variables with a significance threshold $p \leq 0.05$.

Results

The results are expressed epidemiologically, clinically and biologically.

Epidemiological data

• Characteristics of study population

The study population consisted of 35 chronic hemodialysis patients, 57 % of whom were men and 43 % women, a sex ratio of 1.33. The mean age of the patients was 48.97 ± 14.95 years with extremes of 17 and 73 years. The age group 50 to 59 was the most represented (28.6 %) followed by the age group 40 to 49 (20 %) (Figure 1).

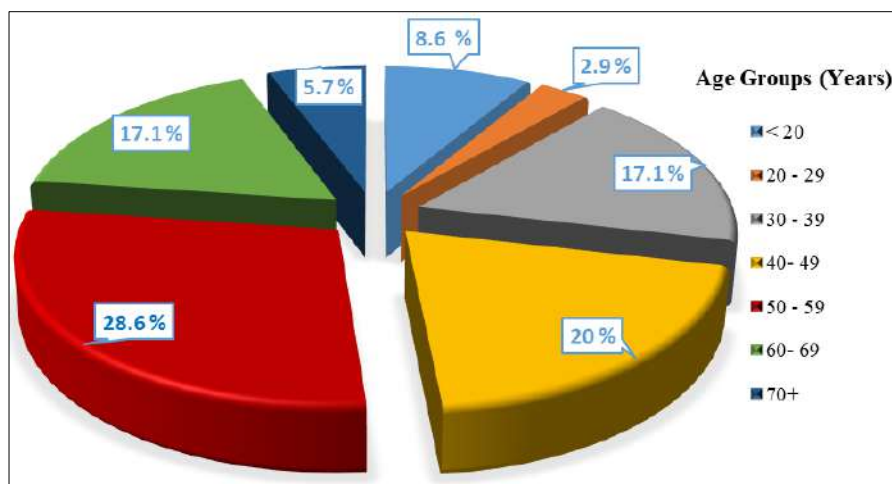


Fig 1: Distribution of population by age group

- Causal lesions**

The first initial nephropathy was nephroangiosclerosis with 40 % of cases followed by chronic glomerulonephritis with

22.9 % of cases, the other pathologies were poorly represented (Figure 2).

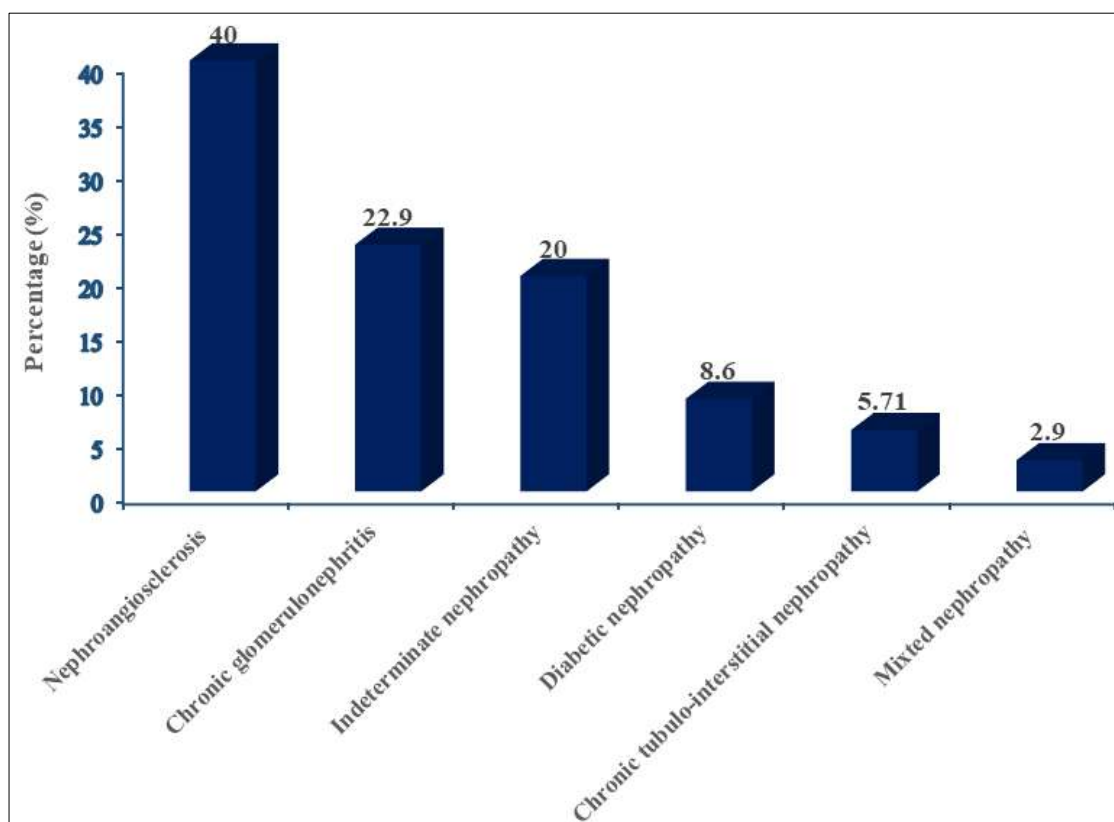


Fig 2: Causal lesions

- History of disease**

Many patients (37.14 %) had no history of disease. High

blood pressure was the leading cause of disease (31.43 %) followed by type 2 diabetes (8.57 %) (Table I).

Table 1: History of disease

History of disease	Numbers	Percentage (%)
Without history	13	37.14
Coxalgia	1	2.86
Diabetes	3	8.57
Benign prostate hypertrophy	1	2.86
High blood pressure	11	31.43
Sickle Cell	1	2.86
Peritonitis	2	5.71
Pyonephrosis	1	2.86
Tuberculosis	2	5.71

Data related to hemodialysis

We were interested in hemodialysis data on the membrane, frequency of dialysis, vascular access and residual diuresis.

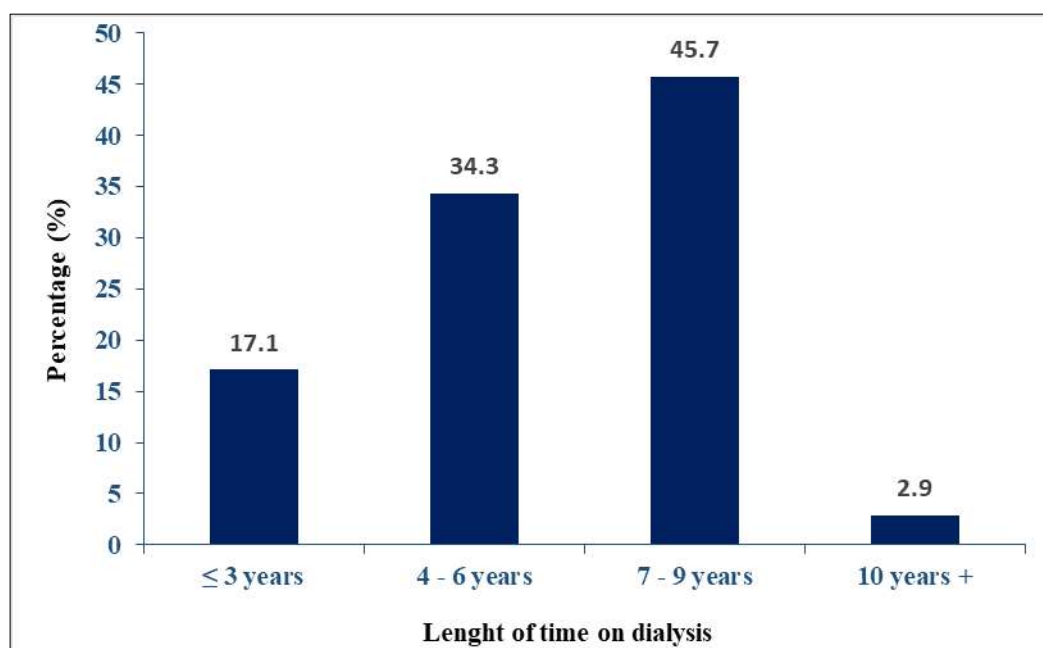
- Membrane type and dialysis rhythm**

The membrane used was the same for all patients. It was a synthetic high flux membrane (NIPRO ELISIO™). All patients had three sessions of 4 hours per week, or 12 hours

of dialysis in total.

- Length of time on dialysis**

The average length of time on dialysis was 5.94 ± 3.03 years with extremes of 1 year and 17 years. 45.7 % of patients who had a length of time on dialysis between 7 and 9 years. Only one patient (2.6 %) had been on dialysis for more than 10 years (Figure 3).

**Fig 3:** Distribution of the population by length of time on dialysis

- Vascular approach**

Thirty-two patients (91.4 %) had an arteriovenous fistula, while 3 patients (8.6 %) dialysed on a temporary venous catheter.

- Residual diuresis**

The majority of patients, 91.4 % of cases, were anuric; only

three patients (8.6 %) had residual diuresis.

Clinical and paraclinical data

- Clinical data**

Clinical symptomatology is dominated by joint pain (48.6 %) (Table II).

Table 2: Clinical Manifestations

Clinical data	Numbers	Percentage (%)
Joint pain	17	48.6
Bone pain	5	14.2
Pathological fractures	2	5.7
Carpal tunnel syndrome	3	8.6
Deaths	2	5.7

- Biological data**

We observed a significant increase in the value of beta 2-microglobulin in the study population with an average of

43.88 ± 16.77 mg / l. The values of the different parameters studied are shown in table III.

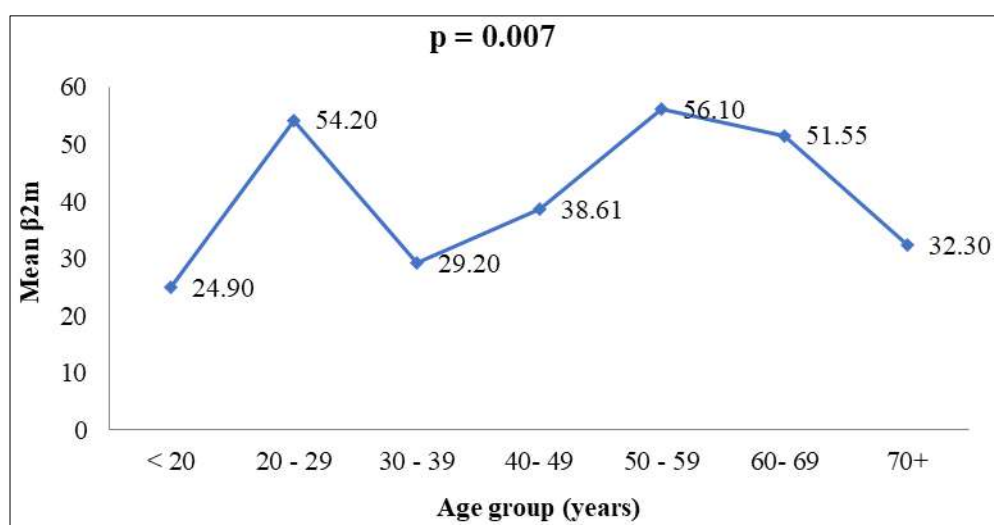
Table 3: Mean values of biological parameters

Biological parameters	Mean values	Reference values
Urea (g/l)	1.51 ± 0.46	0.15 – 0.45
Creatininemia (mg/l)	112.51 ± 44.14	6 – 13
Calcemia (g/l)	89.52 ± 9.04	85 – 105
Phosphoremia (g/l)	40.39 ± 18.36	35 – 55
PTH (pg/ml)	985.29 ± 652.56	15 – 65
Vitamin D (ng/ml)	25.06 ± 8.93	9.3 – 48
CRP (mg/l)	12.60 ± 16.88	< 7
Beta 2-microglobulin (mg/l)	43.88 ± 16.77	1.1 – 2.4

Investigation of correlations between serum concentrations of beta-2-microglobulin ($\beta 2m$) and epidemiological and hemodialysis parameters

- Age and beta 2-microglobulin concentrations**

Figure 4 shows a correlation between age and mean beta 2-microglobulin ($p = 0.007$).

**Fig 4:** Correlation search between age and mean of $\beta 2m$

- Sex and rate of $\beta 2m$**

Females and accumulation of $\beta 2m$ were statistically related ($p = 0.007$) (Figure 5).

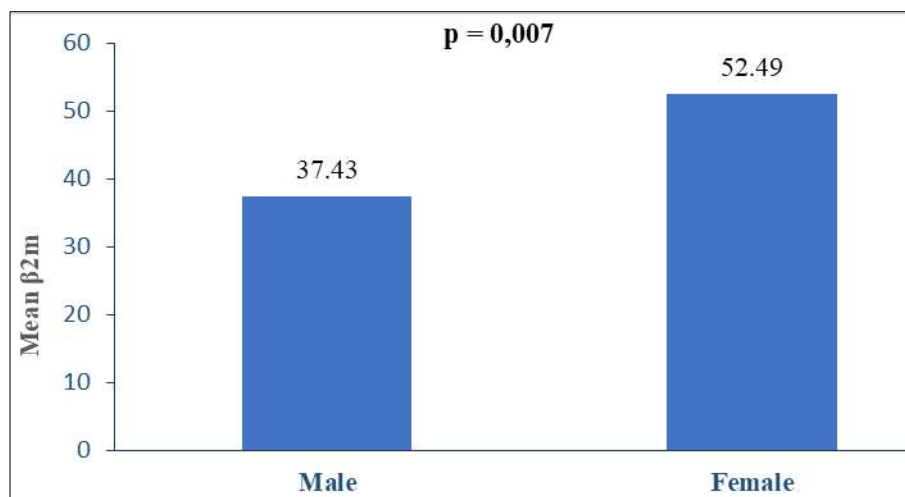


Fig 5: Correlation research between sex and mean of $\beta 2m$

- Length of time on dialysis and the rate of $\beta 2m$**

Figure 6 shows that length of time on dialysis is correlated with the rate of $\beta 2m$ ($p = 0.0001$).

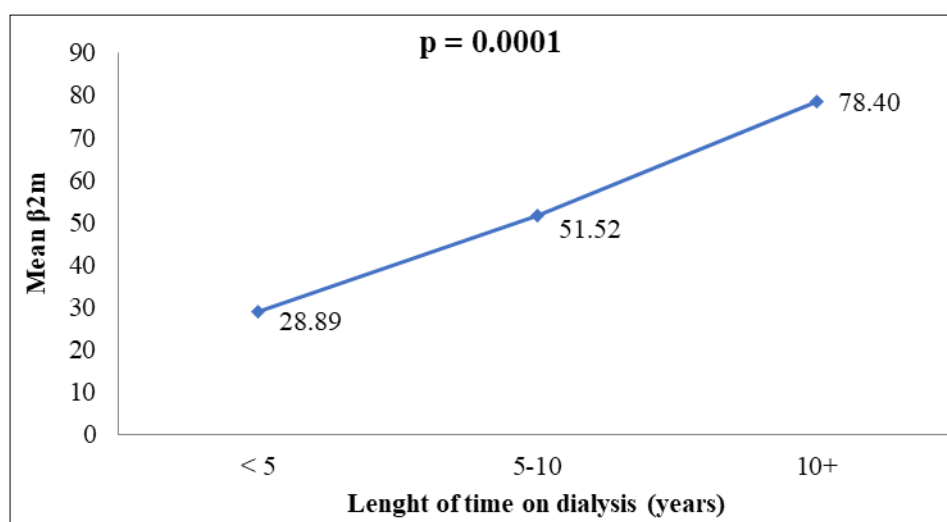


Fig 6: Correlation search between length of time on dialysis and the $\beta 2m$ rate

- Residual diuresis and rate of $\beta 2m$**

We found a statistically significant relationship between the absence of diuresis and the rate of $\beta 2m$ in hemodialysis patients ($p = 0.035$).

However, we did not find a correlation between the history of disease and the $\beta 2m$ rate, either with the initial nephropathy, with the vascular first, or with the biological data.

Discussion

The mean rate of serum $\beta 2m$ reported in our study population is very high, in the order of 43.88 mg / l. High levels of $\beta 2m$ in chronic hemodialysis patients have been reported in the literature [6, 5, 7]. In Morocco, a similar rate (38.42 mg / l) was found in a population of 104 chronic hemodialysis patients [8].

The value of $\beta 2m$ could rise up to 60 times compared to normal due to the bad purification of this molecule by the kidney [2, 5, 7]. In fact, the capacity of the kidney to purify declines with age. It is generally accepted that kidney failure is a disease of older people in developed countries [10]. This contrasts with the results of our study where the average age of our patients is 48.97 years. Our average age is similar to

other African studies carried out in Burkina Faso [9] and Morocco [2] where the average age was 43,54 and 48 years respectively.

Moreover, our study shows that the advanced age of dialysis is a determining factor in the accumulation of $\beta 2m$ in the blood ($p = 0.007$). The work of Van Ypersele ($p < 0.001$) [11], as well as those of Ichkhakh ($p = 0.004$) [8] agree on this fact.

Like age, the female sex was significantly correlated with the value of $\beta 2m$ with a value of ($p = 0.007$). However, some studies [8, 14] could not establish such a correlation. This suggests that this specificity identified in our study is probably due to the relatively advanced age of the female population; although we have noted a clear male predominance with a sex ratio of 1.33. This result is similar to data from studies conducted in Dakar that had regained a male predominance of 55.9 % and 54.4 % with sex ratios of 1.26 and 1.19 [12, 13]. The male predominance of renal failure is thought to be related to several factors, including the higher incidence of some causes of kidney failure in men, and their faster progression in men compared to women [10].

The serum concentration of $\beta 2m$ is significantly elevated in our anuric patients ($p = 0.035$). This finding corroborates the

literature [8, 15]. According to Drueke [16], the highest concentrations of β_2m are found in oligo-urinary uremic patients. A lack of renal elimination of β_2m in these patients would explain its accumulation. Increased β_2m serum concentration is believed to be responsible for amyloid deposition at β_2m in patients [16, 17].

The increase in β_2m was statistically significant with the age of hemodialysis ($p = 0.0001$). The same observation has been made by many authors [18, 19]. The accumulation of β_2m generates a deposit by polymerization in the form of fibrils at multiple organs, and in particular at the joints, which causes amyloidosis. Amylose β_2m is a long-term complication of dialysis. Its frequency and severity correlate with years of dialysis and is accelerated after 30 years of treatment [20]. According to the results of a post mortem study, amyloid deposits of β_2m occur in 21% of cases within two years and in 33 % of cases in four years of dialysis. And this percentage reaches 100 % in dialysis patients for more than thirteen years [18, 19].

However, no correlation was found between the elevation of β_2m and the initial nephropathy, the disease history, the type of vascular first and the biological parameters, as opposed to other studies [8, 21].

In addition, other factors, not taken into account in this study, would be involved in the accumulation of serum β_2m and in the genesis of amyloid deposits at β_2m in chronic hemodialysis, including the biocompatibility of dialysis membranes as well as water quality for hemodialysis and therefore dialysate [2, 7, 22]. The superiority of synthetic membranes of cellulosic membranes with low permeability and biocompatibility, such as cuprophane, has been demonstrated over semi-synthetic cellulosic membranes with high permeability [23].

Conclusion

Serum levels of β_2m are high in our chronic hemodialysis population. Factors such as age, sex, length of time on dialysis and residual diuresis are decisive in increasing the β_2m rate. The measurement of β_2m should be included in the monitoring of chronic hemodialysis.

Acknowledgements

We thank the entire cohort of patients at the hemodialysis unit of the nephrology department of Aristide Le Dantec Hospital for their commitment to participate in our study. Thanks also go to the various services that helped us in the study of our patients.

Conflict of interest

The authors declare that they have no conflict of interest.

Authors contribution

All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.

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