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The risk factors of chronic kidney disease progression in AA amyloidosis

Renal outcome in AA amyloidosis

Refika Büberci, Ayşe Zeynep Bal, Murat Duranay
Department of Nephrology, Ankara Training and Research Hospital, Ankara, Turkey

Abstract

Aim: AA amyloidosis is a disease characterized by the accumulation of protofilaments in the extracellular space as a result of chronic inflammatory disease. The kidneys are the most affected organ. Although the prevalence has decreased due to the advances in treatments, the progression rate to end-stage renal disease (ESRD) is still high. The aim of this study was to determine the risk factors for the progression of chronic kidney disease (CKD) progression in patients with AA amyloidosis.

Material and Methods: Fifty-six patients who were diagnosed with AA amyloidosis as a result of kidney biopsy were included in the study. Demographic features, laboratory data were recorded. Etiological reasons were noted as Familial Mediterranean Fever (FMF) and non-FMF disease. Patients were divided into two groups according to the annual decline of eGFR. Group I consisted of patients whose annual eGFR decline was more than 1ml/min/1,73m2

Results: The mean age of the patients was 51.12±14.5 years. The mean follow-up time was 3.72±3.57years. No difference was found between the two groups in terms of comorbid diseases, age, gender, mean blood pressure. eGFR at baseline was similar. In Group-I, non-FMF diseases were more, proteinuria in 24-hour urinalysis and CRP levels were high, and albumin was low. In regression analysis etiology, proteinuria, LDL-c/HDL-c ratio, platelet-lymphocyte ratio (PLR) are independent risk factors for the annual decline of eGFR.

Discussion: Proteinuria, inflammation and dyslipidemia are important risk factors for CKD progression in AA amyloidosis. PLR is a simple and easy test that reflects inflammation in AA amyloidosis. It is beneficial to closely follow up amyloidosis cases caused by non-FMF disease, such as amyloidosis cases caused by FMF.

Keywords

AA amyloidosis; Dyslipidemia; Inflammation; LDL-c/HDL-c ratio; Proteinuria; Platelet-Lymphocyte ratio

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Corresponding Author: Refika Büberci, Department of Nephrology, Ankara Training and Research Hospital, Ankara, Turkey.
E-mail: refikakaraer@gmail.com P: +90 5052990707
Corresponding Author ORCID ID: https://orcid.org/0000-0003-4737-6681

Introduction

AA amyloidosis is a systemic disease characterized by the storage of amorphous, water-insoluble, proteolysis-resistant protofilaments in the extracellular environment. It occurs as a result of complications of diseases that cause chronic inflammation. Protofilaments originate from the amyloid precursor serum amyloid A (SAA). SAA is an important acute phase reactant biosynthesized in the liver against pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α [1]. While the plasma concentration is 3 mg/l in a normal healthy individual, it may increase up to 1000 mg/l as an acute phase response [2].

The kidneys are the most affected organ in AA amyloidosis. The clinical picture generally starts as proteinuria and over time turns into nephrotic syndrome and end-stage renal disease (ESRD). However, the rate of developing end-stage renal disease is different for each patient. The aim of this study was to determine the risk factors for the progression of chronic kidney disease (CKD) in patients with AA amyloidosis.

Material and Methods

Patients and study design

Fifty-six patients followed between 2010 and 2020 were included in the study. The protocol for the research project has been approved by a suitably constituted Ethics Committee of the institution within which the work was undertaken (Approval number: 15.06.2020/202). All patients had undergone renal biopsy and had been confirmed to have AA amyloidosis. The renal biopsy specimens were stained with hematoxylin and eosin, periodic acid-Schiff, silver methenamine and Masson trichrome for evaluation of glomerular, interstitial, vascular and other pathological changes using light microscopy. Congo-red staining of renal tissue specimens was performed for histopathological diagnosis, and green birefringence was considered to indicate the presence of amyloid deposits. These deposits were confirmed as the AA types of amyloid using immunohistochemical analysis. Patients with primary amyloidosis or NHYA class III and IV heart failure or non-regular follow-up, patients taking anti-coagulant medication, active malignancy and infection, patients who are unwilling to participate in the study were excluded from the study. The endpoints of the study were renal replacement therapy requirement and death in the course of follow-up. The demographic characteristics of the patients, (comorbid diseases (diabetes, hypertension) age, gender, follow-up time) were recorded. Hypertension was determined by physician diagnosis, systolic blood pressure (BP) ≥ 140 mm Hg or diastolic BP ≥ 90 mmHg, or treatment with antihypertensive drugs. Diabetes was determined by physician diagnosis, fasting glucose ≥ 126 mg/dL, or treatment with insulin or oral antidiabetic drugs. Etiological reasons were noted as Familial Mediterranean Fever (FMF) and non-FMF diseases. The diagnosis of FMF was established in accordance with the Tel Hashomer Criteria.

Laboratory analyses

All laboratory data were measured using automated systems and standardized methods. Urea, creatinine, estimated glomerular filtration rate (eGFR), proteinuria level in 24-hour urine at first and last admission to hospital, C-reactive protein (CRP), albumin, uric acid, cholesterol parameters, and complete blood count at first admission to hospital were recorded. On first admission, the patient underwent a kidney biopsy. The last admission was the last outpatient clinic control of patients who did not receive renal replacement treatment and came for regular follow-up, regardless of the CKD stage. CRP, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) parameters were used to evaluate the inflammation status of the patients. NLR was obtained by dividing the absolute neutrophil count by the absolute number of lymphocytes, while the PLR was obtained by dividing the absolute number of platelets by the absolute number of lymphocytes. eGFR was calculated according to the CKD-EPI (CKD Epidemiology Collaboration) equation. The average annual decrease in eGFR was calculated as follow-up times were not the same. It was estimated by the difference between baseline eGFR and the latest available eGFR divided by the time interval in a year. Patients were classified according to the annual change of eGFR as Groups I and II. Group I consisted of patients whose annual decline of eGFR was more than 1ml/min/1,73m2.

Statistical analyses

All data were first checked for normal distribution using the Kolmogorov-Smirnov and the Shapiro-Wilk test. Normally distributed data are presented as the mean± standard deviation. Non-normally distributed data are represented as median (inter-quartile range). Independent samples T-test was used to compare parametric continuous variables between groups. The Mann-Whitney U test was employed for the comparison of non-parametric variables. Pearson's X2 or Fisher's exact were used for categorical variables. Univariate and multivariate Cox regression analyzes were performed to find causes that may affect the annual decline in eGFR. Correlation analysis was used to understand the mechanism of the effects of significant parameters. $P < 0.05$ was considered a significant difference. Analyses were conducted using SPSS Statistics for Windows (version 22.0; IBM Corp, Armonk [NY], United States).

Results

The mean age of the patients was 51.12 ± 14.5 years, and 32 patients were male. The mean follow-up time was 3.72 ± 3.57 years. Familial Mediterranean Fever (FMF) was the most common cause of AA amyloidosis with a frequency of 50%. Non-FMF diseases include infections (14.3%), cancer (10.7%), unidentified factors (10.7%), rheumatoid arthritis (7.1%), inflammatory bowel disease (3.6%), and ankylosing spondylitis (3.6%), respectively. The etiology of cancer patients were head and neck cancer (n:2), colon carcinoma (n:2), basal cell carcinoma (n:2). In these patients, chemotheropathic agents that affect eGFR were not used. At first admission the number of CKD patients with stage 1, 2, 3, 4, 5 are 17, 15, 15, 6, 3, respectively. At the last admission, these numbers changed to 13, 9, 10, 12, 12, respectively. In other words, stage 4 CKD patients increased by 100 %, stage 5 CKD patients increased by 300 % numerically. There were no differences between the two groups in terms of comorbid diseases such as diabetes mellitus (DM) and hypertension (HT), or in terms of age, gender and mean blood pressure (MBP). Baseline levels of urea, creatinine, eGFR at the start of the study was also similar. However, after

Table 1. Comparison of demographic and laboratory data between groups

Parameters	All Patients (n:56)	Group I (n:33)	Group II (n:23)	P
Gender (female) (%)	42,9	33.3	56.5	0.085
Age (years)	51.12±14,5 (min:21-max:80)	52.18±15.15	49.6±13.7	0.519
Etiology(non-FMF) (%)	48.2	63.6	21.Haz	0.006
DM (%)	5.Nis	6.Oca	4.Mar	0.635
HT (%)	21.Nis	21.Şub	21.Tem	0.962
Follow-up time (years)	3.7±3.5 (min:1.5- max:10)	2 (5.75)	2(7)	0.947
MBP (mmHg)	81.6±10.1 (min:70-max:107)	80 (20)	80 (10)	0.953
Annual decline of eGFR (ml/min/1,73m2)	-10.6±27.06 (min:-85 - max: 36.05)	-20.69 (35.22)	2.4(8.4)	0.000
Urea at first admission (mg/dL)	45.28±28.75 (min:11-max:152)	41 (32)	34 (11)	0.08
Creatinine at first admission (mg/dL)	1.55±1.17 (min:0.4-max:6.62)	1.17 (0.85)	1.14 (1.12)	0.816
Proteinuria at first admission (mg/day)	6166±5257 (min:100-max:20275)	6684 (9007)	3012 (6632)	0.008
eGFR at first admission (ml/min/1,73m2)	69.8±36.9 (min:9-max:102)	71.85±37.6	67±36.6	0.637
Urea at last admission (mg/dL)	66.1±49.2 (min:12-max:183)	80.6(70.5)	35 (26)	0.000
Creatinine at last admission (mg/dL)	2.94±2.81 (min:0.3-max:12.34)	2.45 (4.4)	0.98 (1.02)	0.000
Proteinuria at last admission (mg/day)	3808±4669 (min:100-max:20113)	2591 (5739)	1100 (3432)	0.027
eGFR at last admission (ml/min/1,73m2)	53.25±42.1 (min:4.64-max:92)	21 (45.5)	86.9 (58.8)	0.000
Glucose (mg/dl)	92.7±27 (min:70-max:250)	87 (8.5)	91 (9)	0.199
TC (mg/dL)	201.87±78.11 (min:61-max:473)	210.8±92.3	189±50.46	0.307
HDL (mg/dL)	44.21±26.18 (min:19-max:85)	42 (21.5)	40 (9)	0.881
LDL (mg/dL)	121.7±69.6 (min:24-max:382)	105 (119)	97 (33)	0.414
TG (mg/dL)	187.8±105.5 (min:42-max:531)	168 (148.5)	149 (155)	0.993
Non-HDL (mg/dL)	157.6±79.5 (min:63-max:423)	164.2±96.3	148.2±46.5	0.466
TC/HDL	4.96±1.95 (min:0.71-max:14.33)	5.06 (2.34)	4.4(1.59)	0.538
TG/HDL	4.88±3.13 (min:0.36-max:15.62)	4.4 (4.53)	3.68 (3.6)	0.848
LDL/HDL	3.01±1.71 (min:0.15-max:12.07)	2.9 (1.35)	2.74 (1.12)	0.128
TG/non-HDL	1.21±0.66 (min:1.24-max:2.81)	1.2 (1)	1.08 (1.06)	0.671
Uric acid (mg/dL)	5.72±1.23 (min:3-max:7.90)	5.87±1.17	5.5±1.3	0.277
Albumin (g/dl)	2.96±1.05 (min:1.05-max:8)	2.71±1.04	3.33±0.97	0.028
CRP (mg/L)	4.28±6.98 (min:0.2-max:32)	2.8 (4)	1.2 (2.3)	0.043
WBC (106/L)	9604±2662 (min:3900-max:16100)	9972±2817	9077±2382	0.219
Neutrophils (106/L)	6468±2243 (min:2000-max:12000)	6844±2414	5929±1893	0.134
Lymphocytes (106/L)	2214±800 (min:960-max:4200)	2100 (1070)	2000 (790)	0.934
Platelet (106/L)	373089±154614 (min:89000-max:962000)	397000 (213000)	313000 (241000)	0.382
MPV(fL)	8.61±1.32 (min:6.1-max:11.3)	8.56±1.39	8.7±1.25	0.694
NLR	3.24±1.49 (min:1-max:7.79)	3.46±1.68	2.94±1.14	0.202
PLR	184.5±112.1 (min:55.37-max:843.86)	178.2 (96.6)	148.4 (79.9)	0.234
Hemoglobin(g/dL)	12.53±2.28 (min:6.8-max:17.2)	12.55±2.25	12.51±2.39	0.957
RDW-CV (%)	17.53±9.13 (min:12.8-max:31.2)	16 (3)	16.6 (4.3)	0.424

Normally distributed data are presented as mean± standard deviation. Non-normally distributed data are represented as the median (inter-quartile range)
DM: Diabetes mellitus, HT: hypertension, MBP: Mean Blood Pressure, CRP:C-reactive protein, eGFR: Estimated Glomerular filtration rate, WBC: White blood cell, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, MPV: Mean Platelet Volume, RDW: Red cell distribution width TC: Total Cholesterol, TG: Triglyceride, FMF: Familial Mediterranean Fever

Table 2. Univariate and multivariate Cox regression analysis of risk factors affecting annual decline of eGFR

Parameters	UNIVARIATE ANALYSIS			
	β	HR	95%CI	P
Gender	-0.513	0.599	0.288-1.243	0.169
Age	0.02	1.Şub	0.995-1.046	0.120
DM	-0.671	0.511	0.120-2.171	0.363
HT	-0.465	0.628	0.269-1.466	0.282
Etiology	-1.449	0.235	0.109-0.505	0.000
Proteinuria1	0.000	1	1.Oca	0.001
Proteinuria2	0.00	1	1.Oca	0.000
Albumin	-0.450	0.638	0.471-0.864	0.004
CRP	0.081	1.085	1.032-1.140	0.001
WBC	0.000	1	1.Oca	0.149
NLR	0.249	1.283	1.003-1.642	0.048
PLR	0.004	1.004	1.002-1.007	0.000
Hemoglobin	-0.114	0.892	0.751-1.060	0.195
RDW	0.039	1.Nis	1.009-1.072	0.011
Platelet	0.000	1	1.Oca	0.002
MPV	0.205	1.228	0.897-1.681	0.201
TC	0.005	1.005	1.Oca	0.057
HDL	0.004	1.004	0.992-1.016	0.492
LDL	0.008	1.008	1.004-1.013	0.001
TG	0.001	0.999	0.996-1.002	0.676
non-HDL	0.004	1.004	0.999-1.009	0.114
TC/HDL	0.187	1.025	0.995-1.459	0.056
TG/HDL	0.004	0.996	0.902-1.1	0.936
LDL/HDL	0.313	1.368	1.151-1.626	0.000
TG/non-HDL	0.329	0.720	0.424-1.221	0.223
Parameters	**MULTIVARIATE ANALYSIS**			
	β	HR	95%CI	P
Etiology	-1.248	0.287	0.128-0.644	0.002
Proteinuria2	0.000	1	1.Oca	0.049
PLR	0.005	1.005	1.002-1.007	0.001
LDL/HDL	0.257	1.293	1.051-1.591	0.015

Proteinuria1: Proteinuria at first admission, Proteinuria2: Proteinuria at last admission, DM: Diabetes mellitus, HT: hypertension, CRP:C-reactive protein, WBC: White blood cell, NLR: neutrophil/ lymphocyte ratio, PLR: platelet/ lymphocyte ratio, MPV: Mean Platelet Volume, RDW: Red cell distribution width TC: Total Cholesterol, TG: Triglyceride

follow-up, urea and creatinine levels were were significantly higher, and eGFR was significantly lower in Group 1. The annual decline in eGFR was also significantly higher in Group 1. Non-FMF diseases were more, albumin level was low, proteinuria in 24-hour urinalysis at first and last admission, and CRP levels were high in Group I. Cholesterol parameters, cholesterol ratios, and complete blood count parameters were similar between groups (Table-1). In multivariate regression analyses, we found that PLR, etiology (non-FMF diseases), proteinuria at first admission and LDL/HDL ratio are independent risk factors of annual decline of eGFR. (HR:1,05, HR:0,287, HR:1, HR:1,293, respectively) (Table-2). To understand the effect of PLR on annual decline of eGFR, we performed correlation analysis. A positive correlation between PLR and proteinuria at first admission, CRP and NLR was found (r:0.319, p:0.016; r:0.461, p<0.001; r:0.560, p<0.001, respectively). We classified patients into two groups as FMF and non-FMF according to their etiology. Proteinuria at first admission, CRP and PLR levels were high in the non-FMF group compared to the FMF group (Table-3).

Table 3. Comparison of demographic and laboratory data between FMF and non-FMF disease group

Parameters	FMF Group (n:29)	Non-FMF disease Group (n:27)	p
Gender			
Female (%)	%54.2	%45.8	0.757
Male (%)	50%	50%	
DM (%)	%66.7	%33.3	0.527
HT (%)	75%	25%	0.064
Age (years)	44 (21)	56 (24)	0.001
Follow up time (years)	4 (6.75)	1 (2.75)	0.002
MBP (mmHg)	83 (18.5)	80 (10)	0.041
Glucose (mg/dL)	89 (8.5)	86 (9)	0.040
eGFR at first admission (ml/min/1,73m2)	79.48±35.97	59.55±15.82	0.043
eGFR at last admission (ml/min/1,73m2)	63 (72.75)	20 (57.7)	0.002
Proteinuria at first admission (mg/day)	2268(5630)	8710(9391)	<0.001
Proteinuria at last admission (mg/day)	1215 (3637)	2500 (7187)	0.060
Albumin (g/dL)	3.6 (0.9)	2.4 (1.5)	<0.001
WBC (106/L)	9361±2779	9866±2555	0.483
Neutrophils (106/L)	6153±2289	6808±2183	0.279
Lymphocytes (106/L)	2254±805	2170±808	0.697
Platelet (106/L)	274000 (213000)	408000 (187000)	0.029
MPV (fL)	8.6 (1.25)	9.1 (2.5)	0.460
NLR	2.95±1.22	3.56±1.70	0.125
PLR	137(53.37)	191 (79.56)	0.001
CRP (mg/L)	1.1 (1.73)	3.2 (4)	<0.001
RDW (%)	15.5 (3.2)	16.6 (3.8)	0.065
Hemoglobin (g/dL)	12.68±1.85	12.37±2.70	0.624

Normally distributed data are presented as mean± standard deviation. Non-normally distributed data are represented as the median (inter-quartile range)
DM: Diabetes mellitus, HT: Hypertension, MBP: mean blood pressure, eGFR: Estimated Glomerular filtration rate, CRP:C-reactive protein, WBC: White blood cell, NLR: neutrophil/ lymphocyte ratio, PLR: platelet/ lymphocyte ratio, MPV: Mean Platelet Volume, RDW: Red cell distribution width, FMF: Familial Mediterranean Fever

Discussion

AA amyloidosis is a systemic disease resulting from complications of diseases that cause chronic inflammation. The prevalence has decreased from 8.5% to 1.3% due to the advances in treatments [3,4]. However, the progression rate to ESRD is still high. According to the biopsy registry data of the Japan Nephrology Association, 26 (9.2%) of 281 renal amyloidosis patients had stage 5 CKD at the time of diagnosis [4]. According to the 2019 registry of the Turkish Society of Nephrology, amyloidosis is involved in the etiology in 1.89% of hemodialysis (HD) and 1.79% of peritoneal dialysis (PD) patients [5]. In the current study, four of the 56 patients had stage 5 CKD at the time of first admission, this number increased to 14 after 3,7 years of follow-up. Seven patients had begun dialysis. In the regression analysis, it was found that inflammation, proteinuria, dyslipidemia, and non-FMF diseases are independent risk factors affecting the annual decline of eGFR.

Inflammation during renal progression in patients with amyloidosis has both direct and indirect effects. Circulating pro-inflammatory cytokines directly stimulate endothelial and leukocyte cells in the kidney. Reactive oxygen radicals and new pro-inflammatory mediators are released. These substances disrupt the endothelial structure in the kidney and activate the coagulation system. Subsequently, the microvascular response created by the kidney against changes in circulation is disrupted and damage occurs in the nephrons [6]. Indirectly, increased pro-inflammatory cytokines, especially IL-6, accelerate the accumulation in the kidney by increasing serum amyloid-A (amyloid precursor) production [1]. In particular, the deposition in the glomeruli leads to the disruption of the glomerular filtration barrier, and the progression of proteinuria ultimately results in acceleration of renal fibrosis [7].

Another feature of the increased IL-6 in AA amyloidosis is that it increases the platelet level by increasing the production of thrombopoietin in the liver [8]. Previous publications reported that elevated platelet and PLR were independently associated with all-cause mortality risk in cancer patients [9], patients with heart failure [10], pulmonary embolism [11], hemodialysis and peritoneal dialysis patients [12,13]. There is a limited number of studies investigating the effect of PLR on CKD progression. In a study conducted with stage 3-5 non-dialysis, 165 geriatric CKD patients, the effect of PLR on renal progression was not found [14]. However, Binnetoglu E et al. demonstrated a significant correlation between PLR and proteinuria in patients with stage 3-4 CKD [15]. In the current study, it was determined that PLR affects the annual decline in eGFR in both univariate and multivariate Cox regression analysis. Correlation analysis also showed that this effect was due to both inflammation and proteinuria.

Dyslipidemia plays a role in the development of CKD by causing not only atherosclerosis in the microcirculation, but also direct inflammation. Excessive accumulation of free fatty acids (FFA) in tubule cells causes lipoproteins to undergo structural changes, which eventually trigger apoptosis. The SLC27A2 gene is known to play a role in this mechanism [16]. In addition, tubule cells require ATP for reabsorption. The highest level of ATP is produced during the breakdown of fatty acids in the mitochondria. However, excessive breakdown of these fatty acids leads to the production of reactive oxygen radicals and subsequent renal damage [17]. Decreased HDL-c levels and diminished cholesterol efflux capacity are the underlying reasons for the excessive accumulation of FFAs and lipoproteins in the kidneys of CKD patients [18]. LDL, especially oxidized LDL levels, also play a role in the pathogenesis by increasing IL-6 release from macrophages and lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) production [19]. Activation of this receptor induces production of adhesion molecules, cytokines and the release of reactive oxygen species via NADPH oxidase. Besides experimental studies, clinical studies reported the effect of lipid parameters on CKD progression. In a study conducted with 48054 participants, total cholesterol, triglyceride, non-HDL-c, triglyceride/HDL-c ratio, LDL-c/HDL-c ratio were higher in CKD group compared to control group. Regression analysis revealed that triglyceride/HDL-c ratio and non-HDL-c/HDL-c ratio play a role in CKD progression (OR1,21;1,14, respectively) [20]. In a meta-analysis, high intensity statins were found to improve decline in eGFR in populations with CKD not requiring dialysis compared to controls [21]. The current study found that the LDL-c/ HDL-c ratio affects the annual decline of eGFR (HR:1.29)

Proteinuria has been established as a marker of kidney damage in experimental studies and has been widely reported to be a predictor of long-term disease progression at all stages of kidney disease. Guidelines for the evaluation and management

of CKD have already emphasized the importance of assessing albuminuria and proteinuria, in addition to the use of estimated GFR, for disease classification and risk stratification [22]. Similar to our study, the correlation between proteinuria and an annual decline in eGFR has been shown in various studies, and meta-analyses. Astor B C et al. found a strong graded association between proteinuria and risk of ESRD, and an 8-fold higher proteinuria was significantly associated with ESRD (HR 3.42, 95% CI 1.84–6.37) [23]. In a meta-analysis, it was reported that more than 1 gr/day proteinuria had an effect on the progression of stage 3-5 CKD patients to ESRD (HR:1,64 (1,01-2,66) [24].

Finally, in our study, we determined that non-FMF diseases play a role in the progression of CKD. Proteinuria and inflammation, which were higher in the non-FMF group compared to the FMF group, are important underlying reasons.

The limitations of our study are that it is a retrospective study, the sample size is small and IL-6 and SAA levels were not measured. Drugs and drugs compliance were not evaluated.

In conclusion, proteinuria, inflammation and dyslipidemia play an important role in the progression of CKD in AA amyloidosis patients. PLR and LDL-c/ HDL-c ratio are simple and easily applied tests that reflect CKD progression in AA amyloidosis. It is beneficial to closely follow up amyloidosis cases caused by non-FMF disease, such as amyloidosis cases caused by FMF.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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