

# The Role of Interferons in Cardiac Remodeling after Acute Myocardial Infarction

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## ABSTRACT

**Objective:** To determine the relationship of serial interferon (IFN) measurements and adverse cardiac remodeling (AR) after myocardial infarction (MI).

**Study Design:** Observational multi-centre study.

**Place and Duration of Study:** Departments of Cardiology of Diskapi Yildirim Beyazit Training and Research Hospital, Ataturk Training and Research Hospital, Numune Training and Research Hospital, and Dr. Nafiz Sincan Korez State Hospital, Turkey, from June 2015 to June 2020.

**Methodology:** Forty-seven patients with acute MI were included. IFN levels were measured on the first day and at 14 days and 45 days post-MI. Reverse cardiac remodeling (RR) and AR were defined as the reduction of left ventricular end-diastolic volume by  $\geq 12\%$  and increases of  $\geq 12\%$  by cardiac magnetic resonance imaging at the 6-month follow-up. Statistical significance was accepted as  $p < 0.05$ .

**Results:** Median IFN- $\alpha$  (50.1 vs. 34.8 pg/mL,  $p = 0.035$ ), IFN- $\beta$  (39.1 vs. 23.0 pg/mL,  $p = 0.013$ ), and IFN- $\gamma$  (26.7 vs. 18.5 pg/mL,  $p = 0.023$ ) levels on the first day post-MI were higher in the AR group compared to the RR group. At 14 days post-MI, IFN levels had decreased in the AR group, while they had not changed in the RR group. At 45 days post-MI, IFN levels were similar between the AR and RR groups. High IFN- $\alpha$  level on the first-day post-MI was an independent predictor of AR (OR: 1.23, 95% CI: 1.06-1.43,  $p = 0.008$ ).

**Conclusion:** High IFN levels in the acute phase post-MI are associated with AR. Among IFNs, IFN- $\alpha$  is an important predictor of AR. Stable IFN levels appear to be associated with cardiac healing.

**Key Words:** Cardiac remodeling, Interferons, Inflammation, Myocardial infarction.

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## INTRODUCTION

Adverse cardiac remodeling (AR) after acute myocardial infarction (MI) is a major determinate for the development of heart failure and it differs during follow-up in patients who receive similar medical and interventional treatments.<sup>1</sup> Inflammatory response to myocardial necrosis involves the recruiting of monocytes and macrophages in the infarcted area to encourage the removal of tissue remnants and subsequent tissue repair.<sup>2</sup>

Some subsets of macrophages damage the ischemic myocardium, a mechanism based on interferon (IFN)-dependent inflammation. Subsequently, transcriptional differentiations in macrophages facilitate solubilization of scar formation and inflammation. Although numerous signals involved in the regulation of different stages after MI have been reported, the role of IFNs is still not clearly understood.<sup>3</sup>

Currently, it is known that IFNs play roles in processes of innate immunity,<sup>4</sup> and there are two types depending on sequence homology and receptor affinity. Type I IFNs, such as IFN- $\alpha$  and IFN- $\beta$ , are predominantly released by leukocytes and fibroblasts, and IFN- $\gamma$  is the only type II IFN, released mainly by natural killer cells and lymphocytes.<sup>5</sup> Previous research has provided conflicting findings as to whether IFNs are pathological or protective in cardiac remodeling post-MI. Induction of type I IFN signaling, opposing the functions of IFN- $\gamma$ , is positively correlated with beneficial post-MI healing. However, the application of IFN- $\alpha$  disrupted the process of cardiac recovery post-MI.<sup>2</sup>

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These findings showed that unrestrained inflammation can destroy the parenchymal tissue in close proximity, and inflammation can pose an obstacle to appropriate healing and cause secondary necrosis.

Although several studies have evaluated the roles of different types of IFNs in the healing of the myocardium, none of them assessed all three different IFNs in the same patient group. On the other hand, with serial IFN measurements, determination of the period in which excessive IFN release occurs after acute MI may contribute significantly to understanding the pathogenesis of AR. Hence, the aim of this study was to determine the role of IFNs with serial measurements of IFN- $\alpha$ , IFN- $\beta$ , and IFN- $\gamma$  in AR as evaluated by cardiac magnetic resonance (CMR) imaging after acute MI.

## METHODOLOGY

This study was planned as a multi-centre prospective study between June 2015 and June 2020 and designed in line with the revised Declaration of Helsinki (2013, Brazil). Approval for the study was granted by the local ethics committee (2013/106). All of the patients gave informed consent prior to enrollment in the study. Assuming an alpha of 0.05, power of 0.80, and 30% estimated AR rate in line with previous reports, the estimated sample size was at least 40 patients in total.

Patients aged 18-75 years who were admitted to the emergency department with the diagnosis of first STEMI according to the third universal definition of MI,<sup>6</sup> between 8:00 and 12:00 (to prevent the effect of daily rhythm on expression differences of inflammatory markers) and who underwent successful primary percutaneous coronary intervention (pPCI) within the first 12 h of chest pain and did not meet the exclusion criteria were included. The exclusion criteria were patients with late admission, age over 75 years old, failed pPCI, fear of magnetic resonance imaging or claustrophobia, malignant active infection or inflammatory disease, acute or chronic renal or hepatic disease, chronic anti-inflammatory drug use, pregnancy or history of delivery within the last three months, state of cardiogenic shock, right coronary artery occlusion, need for intra-aortic balloon pump, history of previous MI, and subsequent emergency or elective coronary artery bypass grafting according to angiography results and logistical reasons. In addition, patients with no change or less than 12% change in left ventricular (LV) end-diastolic volume (EDV) as evaluated by CMR imaging at the 6-month follow-up were also excluded.

During the study period, 567 patients were admitted to the emergency department with the diagnosis of first STEMI. Of these, 47 patients properly fulfilled the inclusion and exclusion criteria. All STEMI patients were managed according to the latest guidelines of the European Society of Cardiology.<sup>7</sup>

Clinical, demographic, laboratory, and radiological findings were recorded in a timely manner in patient files during follow-up. Calculation of the Global Registry of Acute Coronary Events (GRACE) score was performed with the official calculator ([www.gracescore.org](http://www.gracescore.org)). After inclusion, follow-up CMR imaging was

performed at 14 days and at 6 months after the index event. The assessment of IFN levels was conducted on the first day, 14 days, and 45 days after the index event. Serum samples were stored at -80°C until assayed. After collecting the serum specimens of the whole sample, parameters were measured with the same device in the same session and by the same laboratory staff in the Tissue Typing Laboratory and Genetic Diagnosis Center of the hospital.

Venous blood samples were taken at first admission and analyzed for complete blood count (CBC) and lipid and cardiac biomarkers. The collected blood sample was centrifuged at 1500 rpm for 10 minutes in order to measure the determined parameters. CBC parameters were measured with a Sysmex XN-1000 hematology analyzer (Sysmex Corporation, Kobe, Japan). IFN quantifications were studied after all samples were collected and run in the same laboratory by the same laboratory technician in a single session with the same device. Serum samples were set out to thaw on ice. The analyses of the IFN concentrations were carried out using a bead-based multiplex immunoassay system (Bio-Plex Pro™ Human Inflammation Assays) as per the guidelines provided by the manufacturer. The formation of different sandwich immunocomplexes on distinct bead sets was measured and quantified using the Bio-Plex® MAGPIX™ System (Bio-Rad Laboratories, Hercules, CA, USA). Bio-Plex Manager v5.0 software (Bio-Rad) was used in the determination of final analyte concentrations. For all statistical analyses, the analyte's minimal detectable value was taken as a substitute to replace any values that proved to be lower than the detection limit of the assay. The coefficients of variation between tests for all inflammatory markers were <15%.

Echocardiographic evaluations were evaluated by 2D transthoracic echocardiography with 4- and 2-chamber apical LV imaging. All obtained images were performed *via* the standard biplane method. The LVEDV and LVESV were evaluated *via* a stack of discs summation where each disc height is performed as a fraction of LV length.

All CMR studies were performed with the same devices (3-T scanner, MAGNETOM Skyra, Siemens Medical Systems, Erlangen, Germany) at all centers and those results were collected as core lab data for assessment by an experienced CMR reader blinded to all patient data and outcomes. The applied imaging protocol was published previously in detail.<sup>8</sup> The imaging protocol of the CMR consisted of acquisition of one 2-chamber view, cine short-axis sections (10-mm intervals for 6-mm slice thickness), and one 4-chamber view. We employed electrocardiogram-gated turbo-fast low-angle shot (turbo-FLASH) sequences to assess the indices of LV systolic function. In this process, the following parameters were applied: echo time (TE) 1.42 ms, repetition time (TR) 39 ms, flip angle 57°, voxel size 1.67 × 1.67 × 6 mm. Assessments of LV EDV and LV end-systolic volume (ESV) were performed using syngo.*via* imaging software (Siemens). Papillary muscles and myocardial trabeculations were included in the ventricular cavity volume. End-diastole and end-systole were defined as the phases of the

cardiac cycle with the largest and smallest ventricular cavities, respectively. LV stroke volume was determined as LV EDV minus LV ESV, while the following equation was used for the calculation of ejection fraction:  $(EF) = [(LV\ EDV - LV\ ESV)/LV\ EDV] \times 100$ . LV reverse remodeling (RR) was defined as the reduction of LV EDV by  $\geq 12\%$  at the 6-month follow-up. A 12% increase was defined as AR.<sup>9</sup>

Statistical analyses were performed using SPSS 20 for Windows (IBM Corp., Armonk, NY, USA). Normality testing was performed with the Shapiro-Wilk test. Normal distributions were shown as mean  $\pm$  standard deviation, non-normal distributions as median (interquartile range (IQR)), and categorical variables as numbers and percentages. Differences in numerical variables between the AR and RR groups were evaluated with the Student t-test or Mann-Whitney U test according to normality distribution. Comparisons of categorical variables were performed with chi-square, Yates correction, and Fisher Exact tests. Changes in CMR parameters were evaluated with paired-sample t-tests or Wilcoxon tests. Changes in IFN levels were evaluated with Friedman analysis and differences between groups were examined by repeated-measures ANOVA. Changes in CMR variables and cytokine levels in the post-MI period are shown by  $\Delta$ . The contributions of IFNs to AR were evaluated by logistic regression analysis. In the regression model, parameters associated with AR were adjusted. The agreement of measurement between echocardiographic and CMR measurements is calculated through Lin's classical concordance correlation coefficient (CCC) by MedCalc Software (MedCalc Software Ltd, Ostend, Belgium). Values of  $p < 0.05$  (\*) were considered significant in statistical analysis.

## RESULTS

A total of 47 subjects (41 (87.2%) male and 6 (12.8%) female subjects; mean age:  $55.7 \pm 7.2$  years) were enrolled in the study. AR was observed in 18 (38.3%) patients at 6 months post-MI. The median cardiac troponin I (cTn-I) levels (49.6 vs. 45.9 ng/L, respectively,  $p = 0.045$ ) and monocyte levels ( $8.8 \pm 1.4$  vs.  $7.8 \pm 1.7 \times 10^9/L$ ,  $p = 0.045$ ) were higher in the AR group compared to the RR group. There were no significant difference in baseline demographic, echocardiographic, and other laboratory findings between the AR and RR groups. The distributions of discharge pharmacological therapy were also similar between the AR and RR groups (Table I). The CCC and 95% confidence interval results for LVEF, LVEDV, and LVESV measurement between echocardiographic and CMR are observed with 0.94 (0.89-0.96), 0.84 (0.77-0.89) and 0.87 (0.82, 0.90) respectively.

LV ejection fraction (LVEF) levels were higher at 14 days compared to 6 months in the RR group ( $46.7 \pm 9.9$  vs. 55 %,  $p < 0.001$ ), while they were lower in the AR group ( $47.3 \pm 11.1$  vs. 42 %,  $p = 0.001$ ). Mean infarct sizes were smaller at 14 days compared to 6 months in the RR group ( $15.5 \pm 6.5$  vs.  $12.5 \pm 5.6$  % of LV,  $p < 0.001$ ) and the AR group ( $20.5 \pm 7.7$  vs.  $17.6 \pm 6.7$  % of LV,  $p < 0.001$ ).

Median IFN- $\alpha$  (50.1 vs. 29.2 pg/mL,  $p < 0.001$ ), IFN- $\beta$  (41.8 vs. 23.0 pg/mL,  $p < 0.001$ ), and IFN- $\gamma$  (21.7 vs. 19.0 pg/mL,  $p = 0.029$ ) concentrations on the first day post-MI were higher in the AR group compared to the RR group. At 14 days post-MI, IFN concentrations were similar between the groups (Table II).

At 14 days post-MI, IFN concentrations had decreased in the AR group, while lower levels were detected at 45 days post-MI. In the RR group, IFN concentrations did not change during the post-MI period (Table II).

The effect of IFNs on the first-day post-MI on AR was investigated with an adjusted logistic regression model. In the regression model, monocytes, cTn-I, and infarct size associated with AR were adjusted. According to this model, a high IFN- $\alpha$  level was an independent predictor of AR (OR: 1.23, 95% CI: 1.06-1.43,  $p = 0.008$ ).

## DISCUSSION

The fate of cardiac remodeling after MI is associated with the inflammatory response. The innate immune response is an important regulator of the cardiac remodeling process. The role of interferons in inflammation is thought to be related to triggering the immune system's protective mechanisms and ensuring intercellular communication.<sup>4</sup>

Several factors such as double-stranded DNA breaks in cardiomyocytes during ischemia contribute to the inflammatory response by inducing type I IFNs.<sup>10, 11</sup> The results of this study showed high baseline levels of IFNs and monocytes in the AR group. Type I IFNs can affect the migration of inflammatory cells and monocytes into the infarction site.<sup>2, 12</sup> Monocytes play a key role in the healing of the infarction area, but excessive monocyte and macrophage accumulation may adversely affect post-infarction recovery.<sup>13</sup> Therefore, excessive IFN responses in the early post-MI period can detrimentally affect healing.<sup>14</sup>

IFN- $\alpha$  was administered subcutaneously for 3 days after MI in a rat MI model and was found to impair ventricular dilation with increased infarction size at 28 days post-MI.<sup>2</sup> It is suggested that IFN- $\beta$  exerts both pro-inflammatory and anti-inflammatory effects by modulating the secretion of cytokines and chemokines that regulate inflammation.<sup>15</sup> Experimental studies have shown that IFN- $\beta$  administration was also associated with reduced inflammation, decreased infarct size, improved ventricular function, and decreased symptoms of heart failure in cases of lesions caused by myocarditis.<sup>15, 16</sup> However, IFN- $\beta$  is an immunomodulatory cytokine that may have negative effects on myocardial repair after injury.<sup>15</sup> In experimental models, it was demonstrated that IFN- $\beta$  attenuated the proliferation of vascular smooth muscle cells and hampered collateral artery growth in mice.<sup>17</sup> IFN- $\gamma$  is a pro-inflammatory protein produced upon activation by antigens, alloantigens, or mitogens. In a clinical study, patients who subsequently developed severe LV systolic dysfunction had very low levels of IFN- $\gamma$  on admission.<sup>18</sup>

**Table I: Demographic and clinical findings of the study population.**

Variables	All population n=47	RR group n=29	AR group n=18	p
<b>Demographic findings</b>				
Age, years	55.7±7.2	56.3±7.6	54.7±6.6	0.462
Gender, n (%)				
Female	6 (12.8)	3 (10.3)	3 (16.7)	0.856
Male	41 (87.2)	26 (89.7)	15 (83.3)	
Smoking, n (%)	20 (42.6)	10 (34.5)	10 (55.6)	0.226
Hypertension, n (%)	19 (40.4)	11 (37.9)	8 (44.4)	0.763
Diabetes mellitus, n(%)	12 (25.5)	7 (24.1)	5 (27.8)	>0.999
SBP, mmHg	123.8±15.2	126±17.7	120.3±9.5	0.161
DBP, mmHg	78.2±13.2	79.2±15.1	76.6±9.6	0.516
HR, beat per minute	73.3±12.2	73.1±14.3	73.6±8.2	0.878
Door-to-balloon time, min	43.1±8.8	44.0±9.1	41.6±8.4	0.379
Symptom-to-balloon time, min	313.1±69.9	318.1±71.2	305.2±69.1	0.546
GRACE score	130.0±30.7	126.1±33.5	136.3±25.0	0.269
<b>Echocardiographic findings</b>				
LVEF, %	45.4±9.9	45.3±9.4	45.6±10.2	0.908
LVEDV, mL	136(117-165)	139(115-167)	135(120-166)	0.759
LVESV, mL	86(54-122)	76(55-121)	95(51-124)	0.930
<b>Coronary angiography findings</b>				
Culprit lesion, n(%)				
LAD	31 (66.0)	18 (62.1)	13 (72.2)	0.541
Cx	16 (34.0)	11 (37.9)	5 (27.8)	
<b>Pre-PCI TIMI flow</b>				
0	30 (63.8)	18 (62.1)	12 (66.7)	0.824
1	6 (12.8)	3 (10.3)	3 (16.7)	
2	7 (14.9)	5 (17.2)	2 (11.1)	
3	4 (8.5)	3 (10.3)	1 (5.6)	
Post-PCI TIMI flow >2, n(%)	45 (95.7)	28 (96.6)	17 (94.4)	>0.999
<b>Laboratory findings</b>				
WBC, ×10 <sup>9</sup> /L	11.3±2.6	11.1±2.4	11.7±2.9	0.446
Neutrophils, ×10 <sup>9</sup> /L	8.6±2.0	8.5±2.0	8.7±2.1	0.767
Lymphocytes, ×10 <sup>9</sup> /L	2.3±0.7	2.4±0.7	2.3±0.6	0.527
Monocytes, ×10 <sup>9</sup> /L	8.2±1.7	7.8±1.7	8.8±1.4	0.029*
Platelets, ×10 <sup>9</sup> /L	331.6±36.6	325.7±35.9	341.1±36.6	0.163
Total cholesterol, mg/dL	191.4±28.3	186.2±27.8	199.9±27.7	0.109
LDL, mg/dL	107.2±26.4	105±26.8	110.9±26.1	0.459
HDL, mg/dL	39.5±7.9	38.3±5.0	41.4±11.0	0.269
hs-CRP, mg/L	24.2 (15.6-31.4)	19.1 (14.6-25.8)	26.3 (17.8-33.0)	0.063
cTn-I, ng/L	47 (43.5-52.4)	45.9 (43.5-47.8)	49.6 (43.8-54.6)	0.045*
<b>Discharge therapy</b>				
ACE/ARB, n (%)	47 (100)	29 (100)	18(100)	-
Beta blockers, n (%)	45 (95.7)	28 (96.6)	17(94.4)	>0.999
Statins, n (%)	44 (93.6)	27 (93.1)	17(94.4)	>0.999
<b>CMR findings</b>				
<b>14 days post-MI</b>				
LVEF, %	46.9±10.2	46.7±9.9	47.3±11.1	0.859
LVEDV, mL	152 (133-185)	158 (133-185)	150 (135-183)	0.484
LVESV, mL	94 (59-133)	84 (61-130)	103 (56-133)	0.974
Stroke volume, mL	72.5±13	70.0±9.4	76.6±16.8	0.138
Cardiac output, mL/min	4.6±1.0	4.4±0.8	4.9±1.3	0.149
Infarct size, % of LV	17.4±7.3	15.5±6.5	20.5±7.7	0.021*
<b>6 months post-MI</b>				
LVEF, %	50 (39-57)	55 (45-58)	42 (38-52)	0.011*
LVEDV, mL	154 (132-186)	139 (129-155)	177 (159-227)	<0.001*
LVESV, mL	79 (61-132)	72 (53-110)	132 (70-164)	0.003*
Stroke volume, mL	74.9±14.5	75.9±11.9	73.3±18.1	0.565
Cardiac output, mL/min	4.7±1.2	4.8±0.9	4.6±1.6	0.589
Infarct size, % of LV	14.4±6.5	12.5±5.6	17.6±6.7	0.007*

Numerical variables are shown as mean ± standard deviation or median (IQR). Categorical variables are shown as numbers (%). Chi-square, Yates correction, Fisher exact, Student t, or Mann-Whitney U- tests were used. \*: p<0.05 shows statistical significance. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; AR, adverse remodeling; CMR, cardiac magnetic resonance; cTn-I, cardiac troponin I; Cx, left circumflex artery; DBP, diastolic blood pressure; LAD = left anterior descending artery; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; PCI, percutaneous coronary intervention; RR, reverse remodeling; SBP, systolic blood pressure.

**Table II: Changes of interferon concentrations in the post-MI period.**

Variables	First day	14 days	45 days	p <sup>2</sup>	Δp <sub>time</sub>
IFN-α					
RR group	29.2 (23.8-34.5)	28.0 (25.5-34.0)	27.6 (23.2-32.6)	0.762	<0.001*
AR group	50.1 (44.3-54.5)	29.1 (27.5-41.5)	25.9 (22.6-29.6)	<0.001*	

p <sup>1</sup>	<0.001*	0.329	0.120		
IFN- β					
RR group	23.0 (17.6-29.7)	22.3±7.5	20.8±6.1	0.450	<0.001*
AR group	41.8 (25.7-47.1)	25.8±7.7	24.0±7.1	<0.001*	
p <sup>2</sup>	0.001*	0.200	0.250		
IFN- γ					
RR group	17.7±6.2	18.8 (14.0-24.2)	18.4±6.5	0.151	<0.001*
AR group	23.1±8.0	18.2 (16.2-20.5)	17.7±5.9	0.004*	
p <sup>2</sup>	0.029*	0.751	0.614		

Numerical variables are shown as median (IQR). Changes of IFN levels were evaluated with Friedman analysis and differences between groups were evaluated by repeated-measures ANOVA. p<sup>1</sup>: Comparison between groups in follow-up (reverse remodeling vs. adverse remodeling). p<sup>2</sup>: Comparison over time in remodeling groups (first day vs. 14 days vs. 45 days). Measurements that differed between follow-up examinations are shown in bold. Δp<sub>time</sub>: Comparison of IFN changes between remodeling groups. AR, adverse remodeling; IFN, interferon; RR, reverse remodeling.

However, an experimental study in transgenic mice showed that overexpression of IFN-γ was associated with LV dilatation and impaired systolic function.<sup>19</sup> These conflicting findings suggest that IFNs may have different mechanisms in inflammation in post-MI periods.

Activation and timing of type I IFN signaling to promote repair of tissue may require sensitive modulation *via* different immune cells. Therefore, it may be necessary to regulate type I IFN responses after acute MI. Furthermore, the expression and time of IFN production, jointly with the specific timing of the action, may be important for appropriate immune responses.<sup>14,20</sup> No previous study involving serial measurements of multiple IFN types, including IFN-α, IFN-β, and IFN-γ, has been identified in the literature. In this study, IFN concentrations on the first-day post-MI were higher in AR patients and then decreased in subsequent serial follow-ups. On the other hand, in the RR group, IFN concentrations remained stable during follow-up after MI. On the 14<sup>th</sup> day post-MI, IFN concentrations were similar in RR and AR patients. In serial follow-ups, IFN-α concentrations were an independent predictor of AR. These findings suggest that a better healing process may be achieved by controlling the increased inflammation in the early stage of the infarction and by stimulating the immune response that remains low in the later period in high-risk patients at risk of AR.

The small size of the study population is the main limitation of this work. Secondly, causality cannot be fully revealed due to the cross-sectional nature of this human study. Another limitation is that there was no healthy control group in this study. That would make it easier to interpret the results of the study by comparing IFN levels.

## CONCLUSION

IFN concentrations on the first-day post-MI were higher in AR patients. Among the IFNs, a high IFN-α level is an important predictor of AR. Stable IFN levels appear to be associated with cardiac healing. These different IFN responses seen in both patient groups will be useful for investigations of the therapeutic effectiveness of interferons in further studies.

## ETHICAL APPROVAL:

The study was approved by the Ankara Yildirim Beyazit University Faculty of Medicine's Non-Drug Clinical Research Ethics Committee (Date: 24/06/2013; No. 2013/106).

## PATIENTS' CONSENT:

Informed consent was obtained from all patients or relatives before the study began.

## COMPETING INTEREST:

The authors declared no competing interest.

## AUTHORS' CONTRIBUTION:

FE: Wrote the paper, data acquisition and analysis, interpretation, critical revision, drafting, and final approval. NE, KE: Conception and design, data acquisition and analysis, interpretation, literature search, critical revision, and final approval.

CO, AK, MG: Data acquisition and analysis, interpretation, drafting, literature search, and final approval.

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