J Rheum Dis 2023;30(2):126-132
https://doi.org/10.4078/jrd.2023.0006
pISSN: 2093-940X, eISSN: 2233-4718

Original Article

The relationship between long-term use of nonsteroidal anti-inflammatory drugs and kidney function in patients with ankylosing spondylitis

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Objective: Although nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment for ankylosing spondylitis (AS), their effect on kidney function remains unclear. This longitudinal study investigated the correlation between long-term NSAID use and kidney function in patients with AS using electronic medical records.

Methods: The electronic medical records of 1,280 patients with AS collected from a single center between January 2001 and December 2018 were reviewed. The Assessment of Spondyloarthritis International Society (ASAS) NSAID Intake Score was used to determine the cumulative dose of all NSAIDs prescribed for a different time intervals. Each ASAS NSAID Intake Score was obtained for intervals of 6 months, 1 year, 2 years, 3 years, 5 years, and 10 years. The correlation between the ASAS NSAID Intake Score and final estimated glomerular filtration rate (eGFR) for each interval was investigated.

Results: The mean ASAS Intake Scores for 6-month, 1-year, 2-year, 3-year, 5-year, and 10-year intervals were 55.30, 49.28, 44.84, 44.14, 44.61, and 41.17, respectively. At each interval, the pearson correlation coefficients were −0.018 (95% CI: −0.031 to −0.006, p=0.004), −0.021 (95% CI: −0.039 to −0.004, p=0.018), −0.045 (95% CI: −0.071 to −0.019, p=0.001), −0.069 (95% CI: −0.102 to −0.037, p<0.001), −0.070 (95% CI: −0.114 to −0.026, p=0.002), −0.019 (95% CI: −0.099 to 0.062, p=0.645), respectively. There was a very weak negative relationship between ASAS Intake Score and eGFR at each interval.

Conclusion: Long-term NSAID use did not correlate with kidney function based on real-world data in patients with AS.

Keywords: Anti-inflammatory agents, non-steroidal, Kidney function tests, Renal insufficiency, chronic, Spondylitis, ankylosing

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory arthritis that primarily affects the spine and sacroiliac joints [1,2]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended as the first-line treatment for patients with AS [3-5]. Therefore, many types of NSAIDs are used for temporary or long-term control of disease activity. In addition, several studies have suggested that long-term use of NSAIDs may slow radiographic progression [6,7].

Received February 12, 2023; **Revised** March 4, 2023; **Accepted** March 6, 2023, **Published online** March 21, 2023

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NSAIDs exert analgesic, anti-inflammatory, and antipyretic effects by inhibiting the cyclooxygenase (COX) enzymes [8]. COX has two isoforms, COX-1 and COX-2, which overlap functionally, but exhibit different physiological functions. COX-1 maintains the basic physiological functions of kidney perfusion and protects the gastric mucosa. COX-2 is involved in the inflammatory response, but importantly, it plays a role in increasing prostaglandin production in environments that require augmentation of renal blood flow [9]. In response to volume contraction, COX-2 expression is upregulated to protect the kidneys. In other words, the inhibition of COX-2 by NSAIDs may lead to nephrotoxicity [10].

NSAID-induced nephrotoxicity includes edema due to sodium retention, hyperkalemia, acute kidney injury (AKI), interstitial nephritis, and hypertension [8,10]. The extensive use of NSAIDs implies that many patients are at risk because NSAIDs are widely regarded as important risk factors that influence kidney function and chronic kidney disease (CKD). Notabley, there are reports that the long-term use of NSAIDs is related to deterioration of kidney function [11-13]. A systematic review reported that high-dose NSAIDs use increases the risk of accelerated CKD progression [12]. In addition, a study among a community-based elderly population revealed that high cumulative NSAIDs exposure is associated with an increased risk of CKD [13]. Although there is no clear information on the duration and dose of NSAIDs that can cause kidney function decline, many nephrologists are concerned about the long-term use of NSAIDs [14].

Patients with rheumatic diseases who respond well to NSAIDs, including patients with AS, are often prescribed NSAIDs for a considerable period of time. Although the majority of patients with AS are young [15], there is always concern that long-term use of NSAIDs may leave them vulnerable to impaired kidney function. The purpose of this study was to determine the effect of long-term NSAID treatment on kidney function from electronic medical records (EMRs) collected over 18 years in patients with AS. We focused on the relationship between NSAID dose and estimated glomerular filtration rate (eGFR) by quantifying the prescribed dose of NSAIDs.

MATERIALS AND METHODS

Data collection

In this retrospective observational study, we enrolled patients with AS who had used EMRs from January 2001 and December 2018 at Hanyang University Seoul Hospital, Seoul, Korea. AS patients met the modified New York criteria [16]. Most of the patients visited the outpatient clinic every 6 months from the first visit. Blood tests, including serum creatinine, erythrocyte sedimentation rate, and C-reactive protein, were performed, along with the evaluation of disease activity and side effects. This study was approved by the Institutional Review Board of Hanyang University Seoul Hospital (HYUH 2018-07-007). This study included only anonymized patient data, and all the studies were performed in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the Institutional Review Board of Hanyang University Seoul Hospital because the study retrospectively reviewed EMRs.

Calculation of eGFR

The eGFR was calculated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation [17] using the outpatient serum creatinine measurement.

Calculation of Assessment of Spondyloarthritis International Society (ASAS) NSAID Intake Score

The patients used various NSAIDs to treat AS. Previous studies have been referenced to calculate the total amount of NSAIDs prescribed to a patient [18]. The ASAS NSAID Intake Score is an indicator of the total NSAID dose used in clinical trials or epidemiologic studies. The calculation method is as follows: NSAID Intake Score=NSAIDs daily dose (equivalent score)×(days of intake during period of interest×days of intake per week)/period of interest in days. The equivalent score is a scale for the dose of NSAIDs. For example, no intake was 0, while 500 mg naproxen was 50, 1,000 gm naproxen was 100, 200 mg celecoxib was 50, and 400 mg celecoxib was 100.

Statistical analysis

Variables are summarized as means±standard deviations or counts (percentages). Statistical significance was set at $p<0.05$. The relationship between eGFR and ASAS Intake Score was confirmed using Pearson correlation. The correlation between the NSAID Intake Score and eGFR for each period (6 months, 1 year, 2 years, 3 years, 5 years, and 10 years) was calculated. As a subgroup analysis, the relationship between eGFR and ASAS Intake Score was investigated by dividing patients into three sections by their age: patients aged 18~40, 40~60, and 60 years or

older (18~40, 40~60, 60~80 yr). R statistical language (version 3.6.1; Vienna, Austria; https://www.R-project.org/) was used for statistical analysis.

RESULTS

Baseline characteristics

Of the 1,280 patients, 1,264 patients with serum creatinine levels and a prescription for NSAIDs were identified in the EMRs. Table 1 presents the baseline patient characteristics. The mean age was 30.23±9.37 years, and the follow-up period was 9.95±3.69 years. The mean serum creatinine level was 0.88±0.34 mg/dL and the eGFR was 112.28±13.66 mL/min/1.73 m^2. Thirty-four (2.69%) patients had an eGFR <60 mL/min/1.73 m^2 at least once during follow-up. Two of them (0.16%) had eGFR <30 mL/min/1.73 m^2 at the last follow-up due to a gradual decrease in eGFR. Changes in eGFR according to the follow-up period are shown in Supplementary Figure 1.

Table 1. Baseline clinical characteristics of 1,280 patients

Variable	No. of patients	Value
Age at diagnosis, yr	1,264	30.23±9.37
Female	1,264	152 (12.0)
Follow-up duration, yr	1,264	9.95±3.69
HLA-B27	1,258	1,210 (96.2)
Eye involvement	1,066	392 (36.8)
Peripheral joint involvement	1,057	434 (41.1)
Creatinine, mg/dL	1,264	0.88±0.34
eGFR, mL/min/1.73 m^2	1,264	112.28±13.66
eGFR <60 mL/min/1.73 m^2 at least once during the follow-up period	1,264	34 (2.69)
eGFR <30 mL/min/1.73 m^2 at least once during the follow-up period	1,264	2 (0.16)

Values are presented as mean±standard deviation or number (%).
eGFR: estimated glomerular filtration rate, HLA: human leukocyte antigen.

NSAID Intake Score and eGFR at each interval

The mean NSAIDs Intake Score in each interval and the mean value of the last serum creatinine and eGFR in each interval were obtained (Table 2). The longer the interval, the lower the mean NSAIDs Intake Score, serum creatinine level, and eGFR in all patients. In all age groups, these values also tended to decrease with increasing intervals (Supplementary Table 1). However, the NSAID Intake Score increased only at 10 years interval in the 40~60 and 60~80 years age groups.

Correlation between NSAID Intake Score and eGFR in each interval

A scatter plot showed the relationship between the NSAID Intake Score and eGFR change for each interval in all patients (Figure 1). In most intervals, NSAID Intake Scores were <100, and eGFR changes were distributed near zero. The scatterplots by age group were also similar to the overall patients (Supplementary Figures 2~4 for patients aged 18 to 39, 40 to 59, and 60 or older, respectively). Table 3 shows the Pearson's correlation analysis between the two variables by interval. In all intervals, the Pearson correlation coefficients were mostly between 0 and −0.1, which were statistically significant ($p<0.05$) but not clinically significant. The Pearson correlation coefficients by age group were also mostly between 0 and −0.1, which were difficult to show clinical significance or were not statistically significant even if it was smaller than −0.1 (Supplementary Table 2).

Patients with an eGFR <60 mL/min/1.73 m^2 at least once during the follow-up period

Table 4 and Figure 2 show the change in eGFR of 34 patients who had an eGFR <60 mL/min/1.73 m^2 at least once during the follow-up period. The mean baseline eGFR was 65.9±18.4 mL/min/1.73 m^2. Two patients had a baseline eGFR <60 mL/min/1.73 m^2 and an eGFR <30 mL/min/1.73 m^2 at the last follow-up. One patient had a baseline eGFR of 45.34 mL/

Table 2. NSAID Intake Score and eGFR at each interval

Interval	6 months interval	1 years interval	2 years interval	3 years interval	5 years interval	10 years interval
Number of intervals	24,902	12,157	5,765	3,613	1,946	592
NSAIDs Intake Score	55.30±39.71	49.28±41.22	44.84±40.56	44.14±40.13	44.61±38.49	41.17±40.04
Serum creatinine*, mg/dL	0.90±0.29	0.90±0.27	0.90±0.17	0.90±0.20	0.89±0.25	0.89±0.33
eGFR*, mL/min/1.73 m^2	109.47±13.24	108.88±13.21	108.05±13.70	107.64±13.14	106.84±13.47	104.28±14.68

eGFR: estimated glomerular filtration rate, NSAIDs: nonsteroidal anti-inflammatory drugs. *Values at the end of interval.

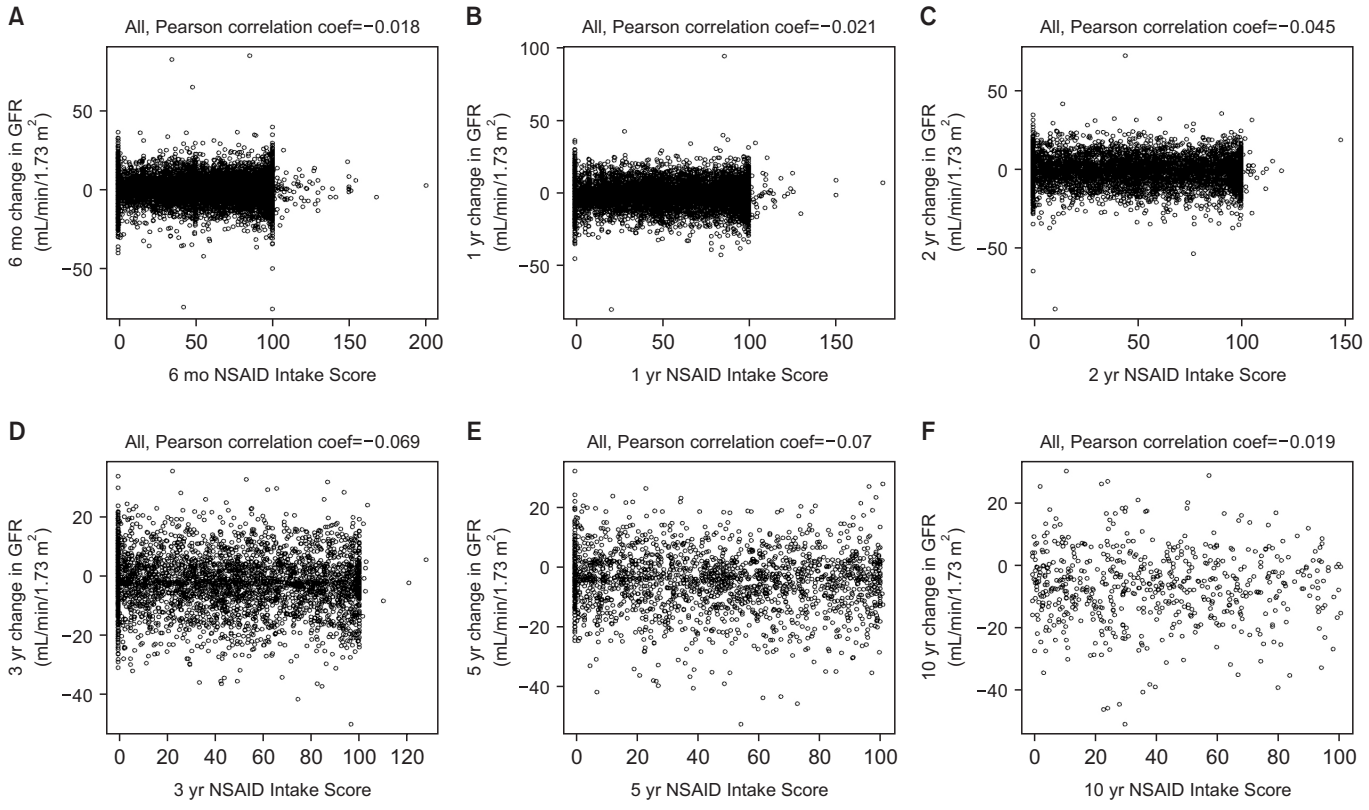

Figure 1. Scatter plots for NSAID Intake Score and eGFR changes in intervals of (A) 6 months, (B) 1 year, (C) 2 years, (D) 3 years, (E) 5 years, and (F) 10 years in overall patients. eGFR: estimated glomerular filtration rate, NSAID: nonsteroidal anti-inflammatory drug.

Table 3. Pearson correlation between NSAIDs Intake Score and eGFR at each interval

Intervals	n	Pearson correlation coefficient	95% CI	p-value
6 months	24,902	−0.018	−0.031 to −0.006	0.004
1 year	12,157	−0.021	−0.039 to −0.004	0.018
2 years	5,765	−0.045	−0.071 to −0.019	0.001
3 yesrs	3,613	−0.069	−0.102 to −0.037	<0.001
5 years	1,946	−0.070	−0.114 to −0.026	0.002
10 years	592	−0.019	−0.099 to 0.062	0.645

eGFR: estimated glomerular filtration rate, NSAIDs: nonsteroidal anti-inflammatory drugs.

min/1.73 m^2, which decreased to 27.43 mL/min/1.73 m^2 after 4,705 days (NSAID Intake Score 91.90). Another patient had a baseline eGFR of 59.87 mL/min/1.73 m^2 and 24.75 mL/min/1.73 m^2 after 3,031 days (NSAID Intake Score of 23.76).

Table 4. Baseline clinical characteristics of 34 patients had eGFR <60 mL/min/1.73 m^2 at least once during the follow-up period

Variable	Value
Age at diagnosis, yr	53.1±12.4
Female	3 (8.8)
Follow-up duration, yr	11.7±3.7
HLA-B27	30 (88.2)
Eye involvement	10 (29.4)
Peripheral joint involvement	14 (45.2)
Creatinine, mg/dL	1.3±0.4
eGFR, mL/min/1.73 m^2	65.9±18.4

eGFR: estimated glomerular filtration rate, HLA: human leukocyte antigen.

DISCUSSION

This study investigated the relationship between NSAIDs and kidney function by using long-term data from patients with AS. The correlation between NSAIDs Intake Score and eGFR change was not significant at intervals of 6 months, 1 year, 2

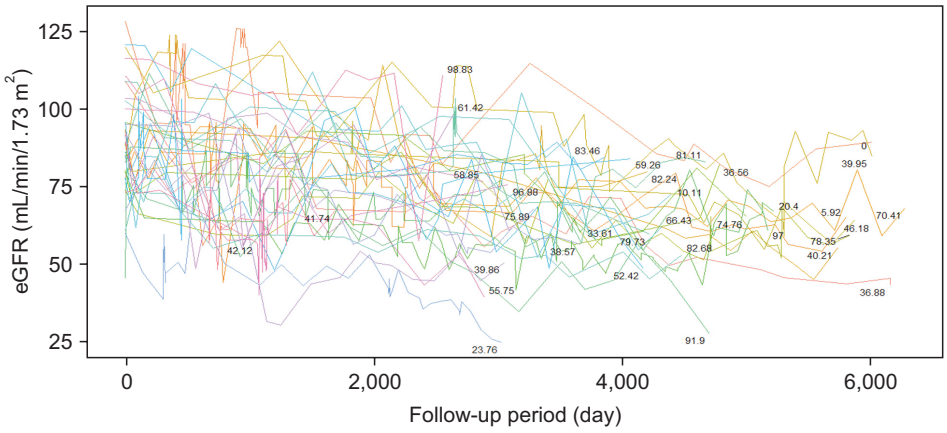

Figure 2. Trend of change of eGFR in patients who have had eGFR <60 mL/min/1.73 m^2 at least once during the follow-up period. The numbers represent the NSAID Intake Score during the follow-up period. eGFR: estimated glomerular filtration rate, NSAID: nonsteroidal anti-inflammatory drug.

years, 3 years, 5 years, and 10 years. Our data provides evidence for the safety of long-term NSAID use in patients with AS without deterioration of kidney function. However, the results should be interpreted with consideration of the characteristics of AS, which is more prevalent at a young age [15].

In AS patients, more patients with impaired kidney function than in the general population may be found due to various factors, such as the presence of comorbidities such as hypertension and nephrotoxic medication. The prevalence rate of AS in patients with decreased eGFR is approximately 0.1%~5.4% [19-21]. In a retrospective cohort, CKD was found in 2.5% of men and 1.6% of women, which was higher than that in men (1.5%) and women (1.2%) in the general population [19]. A single center study among patients with AS in China reported that 5.4% of the patients had reduced eGFR [20]. The risk of renal impairment or CKD seems to be reported differently depending on the definition of kidney disease, methods of kidney function evaluation, and sex and age of the study population. Our data revealed that 2.69% of patients had a decreased eGFR (<60 mL/min/m^2) at least once during the follow-up period. The kidney function of our patients was similar to that of other AS study participants and patients encountered in general medical settings. However, it is worth noting that very few patients showed a sustained decrease in eGFR (<60 mL/min/m^2).

NSAIDs have been widely used as first-line treatment for symptom relief in patients with various types of arthritis. In rheumatoid arthritis (RA), a chronic inflammatory disease, long-term treatment with NSAIDs is often required to control symptoms. Previous studies among patients with RA have reported a relationship between the long-term use of NSAIDs and renal impairment. In a prospective cohort study, chronic NSAID use in patients with RA was an independent predictor of accelerated kidney function decline in patients with an eGFR <30 mL/min/1.73 m^2 [22]. In a population-based cohort study of patients with RA, patients using NSAIDs for more than 90 days had a double risk of CKD compared to non-users [23].

Considering that many patients have been prescribed NSAIDs for a substantial period, the literature regarding the correlation between kidney function and NSAIDs intake in patients with AS is limited. In a single-center cohort study, the use of NSAIDs in patients with AS did not differ between CKD and non-CKD patients [20]. However, this study was insufficient to explain the safety of kidney function in patients with AS requiring long-term treatment with NSAIDs. One age- and sex-matched study of AS reported that the group that used NSAIDs for more than 48 months had a lower rate of kidney dysfunction than those who took NSAIDs for less than 48 months [24]. The authors suggested that these results may be due to AS itself and not to NSAIDs induced nephropathy. However, there was a limitation in that it was difficult to generalize the results because the number of cases (40 cases) was too small.

It is difficult to explain the long-term safety of NSAIDs because of conflicting results on the relationship between NSAIDs and kidney function. However, the subgroup analysis provided reasonable results regarding the stability of NSAIDs in the selected patients. In a cohort study, there was a significant correlation between the cumulative NSAID dose and a decrease in eGFR in elderly patients [13]. Another study reported an increased risk of ibuprofen-associated renal impairment in elderly patients and in patients with coronary artery disease [25]. Among active young and middle-aged adults, modest but significant associations were observed between exposure to high doses of NSAIDs and incident kidney disease [11]. Summarizing those results, caution is warranted with the long-term use of

NSAIDs in patients of old age or with comorbidities. Patients at risk are susceptible to nephrotoxicity owing to their low cardiac output, volume-contracted state, or other conditions that lead to impaired renal perfusion [10]. Considering the age of onset of patients with other arthritic diseases in previous studies, relatively young patients with AS were less likely to have conditions that were more susceptible to NSAIDs-induced nephrotoxicity than patients with other arthritic diseases. We believe that this is why there may have been no association between kidney function and NSAID dose in patients with AS in this study. Therefore, we need to focus on patients with decreased kidney function in the present study. Although their number was small, it is necessary to identify factors that may affect kidney function during long-term NSAID treatment.

In this study, the NSAID Intake Score was used to unify the prescriptions of various NSAIDs into one indicator. Although the defined daily dose system was also used to determine the dose of an NSAID in several studies [13,26,27], the NSAID Intake Score was simple and easy to understand. Interestingly, some patients had NSAID Intake Scores greater than 100. They may have been prescribed more than the regular dose of NSAIDs, or they may have been prescribed two or more overlapping NSAIDs. However, the eGFR change in most patients was less than 20 at all intervals.

The present results should be interpreted in the light of some limitations. First, the long-term use of NSAIDs was calculated by integrating the effects of various NSAIDs into the NSAID Intake Score. Differences in action between NSAIDs, such as the selectivity of COX, were ignored. Second, in patients with AS, there are patients who take NSAIDs when they need them, so it is possible that they were prescribed and did not take the full dose. This was an inevitable limitation of the EMR study, in which compliance was not collected. Third, there were no data on comorbidities such as cardiovascular diseases and diabetes and their associated drugs that directly affect kidney function. Fourth, since most patients with AS were diagnosed at a young age, data on older patients are relatively scarce. Fifth, because patients with initially low renal function tend not to prescribe NSAIDs, these patients could not be included in the study. However, most patients in the cohort, along with a small number of CKD patients, were included in this study, and studies confirming the relationship between early renal function and NSAIDs require a different study design.

We found that long-term NSAID use was not associated with a decline in kidney function, even at 10-year intervals. Moreover, there was no correlation between the duration of NSAIDs use and kidney function among the age groups. These findings suggest that long-term NSAIDs may be safe for kidney function in patients with AS. Further studies are needed to evaluate older patients or those with preexisting conditions, particularly CKD, in a larger patient population.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at https://doi.org/10.4078/jrd.2023.0006.

FUNDING

This work was supported by a National Research Foundation of Korea (NRF) grantfunded by the Korean Government (MSIT) (No. NRF-2021R1C1C1009815).

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported. B.S.K. has been an editorial board member since May 2022, but has no role in the decision to publish this article.

AUTHOR CONTRIBUTIONS

T.H.K. had full access to all of the data used in the study and takes responsibility for the integrity of the data, study supervision, and accuracy of its analysis. Concept and design: B.S.K., S.H., and T.H.K. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: B.S.K., S.H., and T.H.K. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: B.S.K., S.Y.P., and S.H. Obtained funding: B.S.K. Administrative, technical, or material support: B.S.K., J.H.S., and T.H.K. Supervision: T.H.K.

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AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author.

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