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Research Article

Clinical Significance of Systemic Immune-Inflammation Index and Pan-Immune-Inflammation Index in Patients with Metastatic Gastric Cancer

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Abstract

Objectives: Simple, cheap, and effective methods in predicting the prognosis of patients with metastatic gastric cancer (mGC) are still lacking. We aim to investigate whether the systemic immune-index (SII) and pan-immune-inflammation value (PIV) have a prognostic significance in patients with mGC.

Methods: Patients diagnosed with pathological confirmed mGC were included and survival outcomes were evaluated. SII and PIV were calculated with the formula platelet count x neutrophil count/lymphocyte count and platelet count x neutrophil count x monocyte count/lymphocyte count, retrospectively. Cutoff values of SII (low, <730; high, ≥730) and PIV (low, <390; high, ≥390) were determined according to the previous studies.

Results: A total of 60 patients were included the study. The median duration of follow-up was 9.0 (range: 3.0–47) months. Median progression-free survival (PFS) was found 8.2 (95%Confidence Intervals [CI]: 4.5–11.9) months and 6.1 (95% CI: 4.5–7.6) months for SII-low and SII-high groups, retrospectively (p:0.016). Median PFS was 8.2 (95% CI: 5.1–11.3) months in the PIV-low group and 5.6 (95% CI: 4.0–7.2) months in the PIV-high group (p:0.037). Multivariate Cox regression analysis was performed and high-SII was the only independent prognostic factor affecting PFS in a patient with mGC.

Conclusion: SII is a simple, cheap, and useful marker and it may be used in routine clinical practice to predict the prognosis for patients with mGC if validated with prospective studies.

Keywords: Metastatic gastric cancer, Pan-immune-inflammation value, Progression-free survival, Systemic immune-index

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Gastric cancer is the fifth most common cancer in the world and also one of the leading causes of cancer-related deaths. Gastric cancer is more common in men, and some people living in Central and South America, Eastern Europe, and East Asia (China and Japan) are more likely to develop gastric cancer.[1, 2] Although, surgical resection with or without neo (adjuvan) chemotherapy can be curative especially in the early stages, the main reason of treatment failure is that early diagnosis is minimal, with many patients presenting advanced stages. Despite developing new treatment approaches such as chemotherapy regimens, immunotherapies, and targeted therapies, 5-year survival rates are still very low for metastatic gastric cancer (mGC).[3] Despite some molecular tests such as human epidermal growth factor receptor 2, programmed death-ligand 1; and simple, cheap, and effective methods in predicting the prognosis of patients with mGC are still lacking. In daily practice, it is necessary to identify a reliable biomarker to predict the prognosis.

Systemic inflammatory responses play a pivotal role in the tumor microenvironment for tumor development, angio-

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genesis promotion, and metastasis; and some different systemic inflammation-based prognostic scores were described.[4] In recent years, many studies have reported in different solid cancers that the inflammation-related hematological index, such as lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, systemic immune-inflammation index (SII), and pan-immune-inflammation value (PIV), can evaluate the prognosis of cancer patients.[5-9] Among these, the SII and PIV scores seem to be more complex but more reliable to predict the prognosis. SII, which is calculated as platelet count(P) x neutrophil count(N)/ lymphocyte count(L), has been recently shown to have a powerful prognostic value in several tumors including lung cancer, esophageal cancer, colorectal cancer, hepatocellular cancer, and gastric cancer.[8, 10-13] Moreover PIV is calculated as platelet count (P) x neutrophil count (N) x monocyte (M)/ lymphocyte count (L). A recent meta-analysis has shown that the PIV score could be important to predict the prognosis in various solid cancer types including colorectal cancer, malign melanoma, lung cancer, and breast cancer.[14] There are some studies about the relationship between gastric cancer and SII score. To the best of our knowledge, many of these studies are about especially early stages gastric cancers and these studies reported that SII can be a useful tool to predict the prognosis for non-mGC patients.[8, 15-18] However, data are very limited for SII and PIV scores for their prognostic significance in patients with mGC.

In our current trial, we aim to investigate whether the SII and/ or PIV have a prognostic significance in patients with mGC.

Methods

Patients diagnosed with pathological confirmed mGC from two different hospitals in Turkey between 2016 and 2022 were included in our study. We reviewed the patients' file and hospital databases retrospectively, and we recorded the patients' demographic characteristics, and baseline hemogram parameters such as hemoglobine, platelet, neutrophil, monocyte, and lymphocyte count. Survival outcomes were also recorded. Patients were excluded if they met the following criteria: History of regular corticosteroid use for any reason, history of other malignant tumors, lack of blood test results, lost of follow-up, known autoimmune diseases, and active infection at the time of diagnosis. In addition, patients with brain metastases requiring steroid use in treatment were not included in the study due to the effects of steroids on hemogram parameters.

SII, PIV, and NLR were calculated with the baseline hematological parameters of the patients (before the first cycles of chemotherapy). SII was calculated with the formula P x N/L. PIV was calculated with the formula P x N x M/L. NLR was calculated with the formula N/L. In our patients' population, an optimal cutoff value with appropriate sensitivity and specificity could not be found with ROC curves. Optimal cutoff values of SII (low, <730; high, ≥730); PIV (low, <390; high, ≥390); and NLR (low, <3; high ≥3) were determined according to the previous studies.[19-22] Progression-free survival (PFS) was defined as the time between the 1st day of treatment and the day of progressive disease or death from any cause. Overall survival (OS) was defined as the time between the 1st day of treatment and the date of death from any cause. If progression or death had not occurred, PFS and OS were censored at the date of the last follow-up.

All statistical analyses were performed with using Statistical Package for the Social Sciences version 20.0 Software (SPSS, USA). The normality assumptions were controlled by the Kolmogorov–Smirnow test. Descriptive analyses were presented using median (interquartile range) or number(n) and percentage (%), where appropriate. The Mann–Whitney U-test is used to compare whether there is a difference in the dependent variable for two independent groups. Independent categorical variables were compared using the Chi-square test or Fisher exact test. Survival curves were generated by the Kaplan–Meier method and the log-rank test was performed to compare OS and PFS, between the groups. Independent prognostic factors were determined by creating a cox-regression model with parameters with $p<0.05$ in the univariate analysis. A two-sided $p<0.05$ was considered statistically significant.

This research was designed and conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and was approved by the Van Training and Research Hospital Ethics Committee (Approval Date-No: July 20, 2022-2022/16-02).

Results

A total of 60 patients were included the study. In general, the median age was 60 (51–70), and 17 (28.3%) patients were female. The majority of patients (85%) were de novo metastatic. The most common site of metastasis is the liver (40 patients, 66.7%). The baseline characteristics of all patients, SII low and SII high patients groups, are shown detail in Table 1. The baseline characteristics of the patients were similar between the SII low and SII high groups.

The median duration of follow-up was 9.0 (range: 3.0–47) months for all patients, and it was found 10.5 (range: 3.0–46) and 7.1 (range: 3.0–47) months for SII-low and SII-high groups, retrospectively. Median PFS and OS for all patients were found 6.1 (95% Confidence Intervals [CI]: 4.9–7.2 months) and 14.3 (95% CI: 9.3–19.4 months), retrospectively. Median PFS was found 8.2 (95% CI: 4.5–11.9) months and 6.1 (95% CI: 4.5–7.6) months for SII-low and SII-high

Table 1. Baseline characteristics of the patients according to systemic immune inflammation index (SII)

	Total n=60	SII low n=26	SII high n=34	p
Age, year, median (IQR)	60 (51-70)	60 (52-66)	58 (50-71)	0.946
Gender, n (%)				
Female	17 (28.3)	4 (15.4)	13 (38.2)	0.052
Male	43 (71.7)	22 (84.6)	21 (61.8)	
ECOG PS, n (%)				
0-1	41 (68.3)	16 (61.5)	25 (73.5)	0.322
2	19 (31.7)	10 (38.5)	9 (26.5)	
Smoking, n (%)				
Never	30 (50.0)	15 (57.7)	15 (44.1)	0.297
Former/Active	30 (50.0)	11 (42.3)	19 (55.9)	
Her-2 status, n (%)				
Negative	51 (85.0)	21 (80.8)	30 (88.2)	0.482
Positive	9 (15.0)	5 (19.2)	4 (11.8)	
De-novo metastasis, n (%)				
No	9 (15.0)	3 (11.5)	6 (17.6)	0.719
Yes	51 (85.0)	23 (88.5)	28 (82.4)	
Liver metastasis, n (%)				
Yes	40 (66.7)	17 (65.4)	23 (67.6)	0.854
No	20 (33.3)	9 (34.6)	11 (32.4)	
Peritoneal metastasis, n (%)				
Yes	28 (46.7)	13 (50.0)	15 (44.1)	0.651
No	32 (53.3)	13(50.0)	19 (55.9)	
Lung metastasis, n (%)				
Yes	9 (15.0)	6 (23.1)	3 (8.8)	0.157
No	51(85.0)	20 (76.9)	31(91.2)	

n: number, IQR: interquartile range, PS: performance status, Her-2: Human Epidermal Growth Factor Receptor-2.

groups, retrospectively. The median PFS of the SII-high group was statistically significantly shorter than the SII-low group (p=0.016) (Fig. 1). Median PFS was 8.2 (95% CI: 5.1–11.3) months in the PIV-low group (n=25) and 5.6 (95% CI: 4.0–7.2) months in the PIV-high group (n=35). The median PFS of PIV-high group was stastistically significantly shorter than PIV-low group (p=0.037) (Fig. 2). Median OS was found 21.1 (95% CI: 5.2–37.0) months and 10.6 (95%

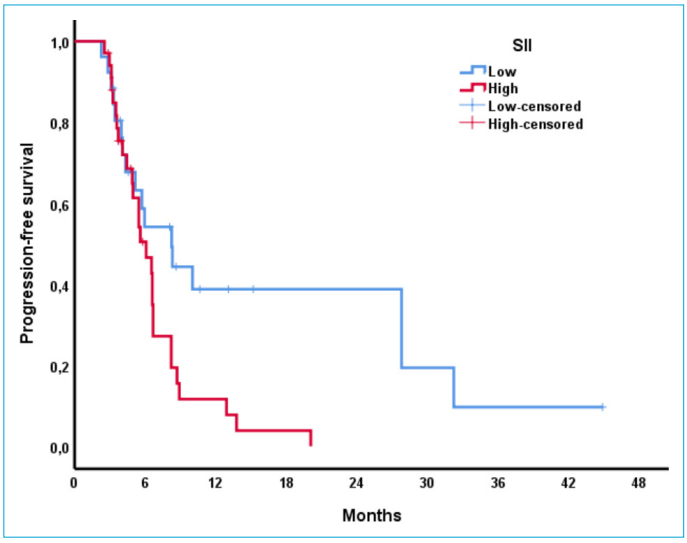

Figure 1. Progression-free survival of patients based on systemic immune-inflammation index.

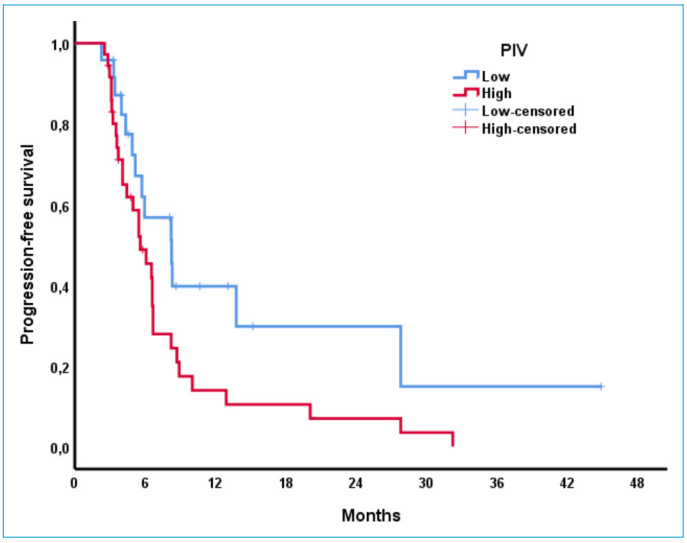

Figure 2. Progression-free survival of patients based on Pan-Immune-Inflammation Index.

CI: 4.8–16.4) months for SII-low and SII-high groups, retrospectively (p=0.062). Furthermore, it was found 21.1 (95% CI: 12.8–29.4) months and 10.6 (95% CI: 6.0–15.2) months for PIV-low and PIV-high groups, retrospectively (p:0.324). There was no overall survival difference between the group when comparing both SII and PIV status (Fig. 3). Moreover, median OS was statistically significance better in patients whose performance status (PS) is 0 or 1 than in patients whose PS is 2. (15.1 months [95% CI: 12.7–17.5] and 6.5 months [95% CI: 5.4–7.6], retrospectively) (p=0.025). Univariate analyses of PFS and OS were demonstrated detail in Table 2.

Multivariate Cox regression analysis was performed to determine independent prognostic factors to affect PFS, and it is shown in Table 3. High-SII was the only independent prognostic factor affecting PFS in a patient with mGC (HR: 2.189, 95% CI: 1.136–4.219) (p=0.019).

Discussion

In our current trial, we found that high SII was an independent predictor of poor prognosis in patients with mGC. Although our study was planned retrospectively, we think that if it is validated with prospective studies, SII is a simple, cheap, and useful marker and, it can be used in routine clinical practice to predict prognosis for patients with mGC.

In our study, there was 60 patients. The median age was 60 (51–70), and 43 (71.7%) patients were male. Median PFS and OS for all patients were found 6.1 (95% CI: 4.9–7.2 months) and 14.3 (95% CI: 9.3–19.4 months), retrospectively. The demographic characteristics and median survivals for our patient groups are consistent with literature data and so reliable.[23-25]

Median PFS was found 8.2 (95% CI: 4.5–11.9) months and 6.1 (95% CI: 4.5–7.6) months for SII-low and SII-high groups, retrospectively. The median PFS of SII-high group was stastistically significantly shorter than SII-low group (p=0.016). Despite no statistical significance, median OS was also found shorter in the SII-high group and they were found 21.1 (95% CI: 5.2–37.0) months and 10.6 (95% CI: 4.8–16.4) months for the SII-low and SII-high groups, retrospectively (p=0.062). In this subject, for gastric cancer, previous studies are generally about pre-operative and neoadjuvant treatment period SII levels and prognosis. In these trials, to sum up, high pre-treatment SII predicted poor survival.[8, 15-17] To the best of our knowledge, there is only one study about mGC. Demir et al. designed a study about the relationship between SII and mGC, and they argued that high SII may be a poor prognostic factor in a patient with mGC, but statistical significance could not be demonstrated in this trial for overall survival (9 months vs. 12 months for SII high and SII low patients groups, retrospectively, p=0.13). PFS was not evaluated in this trial.[26] Although it was not statistically significant in our study, mOS was numerically shorter in the SII high group. In addition, mPFS was found to be significantly shorter in the SII high group, when compared to the SII low group. This situation was shown in both univariate analysis and multivariate cox regression analysis. Hence, we suggest that high SII was an independent predictor for poor prognosis in patient with mGC and it may be used in clinical routine if validated prospectively studies.

The recently developed PIV, an equation including the neutrophil, platelet, monocyte, and lymphocyte levels, has been evaluated in several solid cancers including colorectal cancer, malign melanoma, lung cancer, and

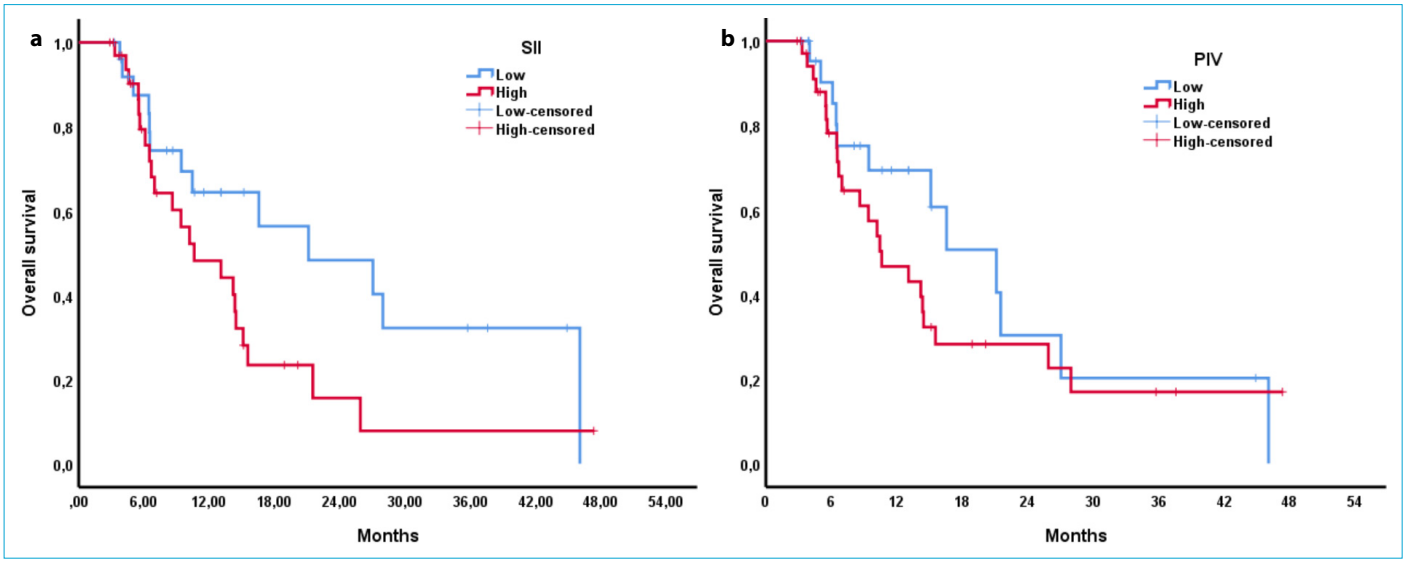

Figure 3. Overall survivals of patients based on systemic immun-index **(a)** and Pan-Immune-Inflammation Index **(b)**.

Table 2. Univariate analysis of PFS and OS

	Median PFS (95% CI)	p	Median OS (95% CI)	p
Total	6.1 (4.9-7.2)	-	14.3 (9.3-19.4)	-
Age, year				
<60	6.1 (4.7-7.5)	0.414	15.5 (12.9-18.2)	0.624
≥60	6.5 (5.2-7.9)		10.2 (5.9-14.5)	
Gender				
Female	5.4 (4.1-6.8)	0.131	13.1 (8.3-17.8)	0.270
Male	6.7 (4.2-9.1)		15.1 (8.3-21.9)	
ECOG PS				
0-1	6.7 (4.7-8.6)	0.364	15.1 (12.7-17.5)	0.025
2	5.0 (4.0-5.9)		6.5 (5.4-7.6)	
Smoking				
Never	5.0 (2.5-7.4)	0.895	13.1 (7.4-18.7)	0.671
Former/Active	6.6 (5.8-7.4)		14.3 (7.9-20.8)	
Her-2 status				
Negative	6.5 (5.5-7.6)	0.900	14.2 (9.2-19.2)	0.135
Positive	5.4 (4.0-6.9)		27.0 (5.3-48.7)	
De-novo metastasis				
No	4.1 (3.1-5.0)	0.132	13.1 (7.7-18.5)	0.287
Yes	6.5 (5.5-7.5)		14.4 (7.1-21.8)	
Liver metastasis				
No	8.7 (3.8-13.6)	0.065	15.5 (6.8-24.3)	0.190
Yes	5.7 (4.7-6.7)		10.4 (4.3-16.6)	
Peritoneal metastasis				
No	6.5 (5.1-8.0)	0.783	14.2 (7.8-20.6)	0.651
Yes	5.9 (4.5-7.4)		14.3 (8.7-20.0)	
Lung metastasis				
No	6.1 (5.0-7.1)	0.868	14.2 (9.3-19.1)	0.965
Yes	8.2 (0-16.8)		15.1 (0-33.4)	
NLR				
Low	6.1 (4.8-7.4)	0.142	21.1 (4.0-38.2)	0.073
High	6.5 (4.6-8.5)		13.1 (7.1-19.1)	
PIV				
Low	8.2 (5.1-11.3)	0.037	21.1 (12.8-29.4)	0.324
High	5.6 (4.0-7.2)		10.6 (6.0-15.2)	
SII				
Low	8.2 (4.5-11.9)	0.016	21.1 (5.2-37.0)	0.062
High	6.1 (4.5-7.6)		10.6 4.8-16.4)	

PFS: Progression-free survival , OS: Overall Survival, CI: Confidence interval, PS: performance status, Her-2: Human Epidermal Growth Factor Receptor-2, NLR: Neutrophil-to-lymphocyte ratio, PIV: Pan-Immune-Inflammation Index, SII: Systemic Immune-Inflammation Index

Table 3. Cox proportional hazards regression model for PFS

	HR (95% CI)	p
PIV		
Low	Ref	0.367
High	1.413 (0.667-2.989)	
SII		
Low	Ref	0.019
High	2.189 (1.136-4.219)	

PFS: Progression-free survival, HR: Hazard ratio, PIV: Pan-Immune-Inflammation Index, SII: Systemic Immune-Inflammation Index.

breast cancer.[14] In our trial, in addition to the SII, we also calculated PIV and evaluated the relationship with survivals. Median PFS was 8.2 (95% CI: 5.1–11.3) months in the PIV-low group and 5.6 (95% CI: 4.0–7.2) months in the PIV-high group. The median PFS of PIV-high group was stastistically significantly shorter than PIV-low group. Median OS was found 21.1 (95% CI: 12.8–29.4) months and 10.6 (95% CI: 6.0–15.2) months for PIV-low and PIV-high groups, retrospectively (p=0.324). Multivariate Cox regression analysis was performed to determine independent prog-

nostic factors to affect PFS. High-PIV was not an independent prognostic factor affecting PFS in patient with mGC. (HR:1.413, 95% CI: 0.667–2.989) (p=0.367). The PIV could be a useful prognostic biomarker for some solid cancers such as colon, esophageal, hepatocellular carcinoma, and breast cancers.[9, 19, 27, 28] Contrary to these findings, PIV is not a significant predictor for clinical outcome measures of advanced melanoma patients under immunotherapy.[29] In our study, although a significant PFS difference was observed between the PIV-high and PIV-low groups in univariate analysis, PIV could not be demonstrated as an independent predictive factor for PFS in patients with mGC in multivariate analysis. As seen above, unlike the SII score, the data on whether PIV predicts survival is conflicting. Further studies are needed.

A large number of studies have reported the relationship between inflammation and tumor development, and it is well-known that neutrophils, lymphocytes, and platelets play an important roles in inflammation and tumor progression. Furthermore, they may reflect the balance of inflammation and immune responses in the body.[30-32] Although the molecular mechanisms underlying the prognostic value of SII is a complex subject, to state simply, neutrophils are an important component of the non-specific immune system and they produce cytokines and chemokines (vascular epithelial growth factor, IL-8, IL-16, etc.) that stimulate tumor cell growth.[8, 32, 33] An interesting hypothesis about platelets has been claimed that they can form a physical shield around cancer cells to protect them from attacks by immune cells.[34] Finally, it is also well-known that lymphocytes are an important component of cellular immunity. They can protect the body against the tumor cells by inhibiting the occurrence and growth of tumor cells.[8, 32, 35, 36] As mentioned before, SII was calculated with the formula P x N/L. Therefore, when SII levels increase; it means that neutrophil or platelet counts increased, or lymphocyte count decreased. That means, the inflammatory factors are stronger than the immune factors, tumor cells can easily survive in this environment, and thus, the risk of poor prognosis is more likely. We also think that this may be the reason why SII can predict the prognosis of mGC.

Retrospective design of our study and a relatively small number of patients can be said most important limitations of our study. Based on some studies in the literature, we take the 730 number as a cutoff value for SII, but the optimal value is not known yet. Prospective and well-design studies with a large number of patients are needed.

Conclusion

SII is a simple, cheap, and useful marker and it may be used in routine clinical practice to predict the prognosis for patients with mGC if validated with prospective studies. High SII was an independent predictor for poor prognosis in patient with mGC.

Disclosures

Ethics Committee Approval: Van Training and Research Hospital Ethics Committee/Approval Date-No: July 20, 2022-2022/16-02.

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Conflict of Interest: None declared.

Authorship Contributions: Concept – Y.I., O.Y.B.; Design – Y.I., O.Y.B.; Supervision – Y.I.; Materials – Y.I., O.Y.B.; Data collection and/or processing – Y.I., O.Y.B.; Literature search – Y.I., O.Y.B.; Writing – Y.I.; Critical review: Y.I., O.Y.B.

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