Fibrinogen Levels and Cognitive Profile Differences in Patients with Mild Cognitive Impairment

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Keywords

Fibrinogen · Mild cognitive impairment · Attention · Vascular pathology

Abstract

Background: Fibrinogen is considered a marker of vascular pathology, indicating a weakened blood-brain barrier, and has a causative role in neuroinflammation and neurodegeneration. Little is known about the relationship between fibrinogen levels and cognitive function in patients with mild cognitive impairment (MCI). We aimed to investigate differences in cognitive profiles according to plasma fibrinogen levels in patients with MCI and the influence of plasma fibrinogen levels on cognitive decline. **Methods:** This retrospective cohort study included 643 patients with MCI: 323 patients in the high fibrinogen (high fib) group and 320 patients in the low fibrinogen (low fib) group. A multiple linear regression model was performed to compare cognitive test performance between groups. The Cox proportional hazard model was used to analyze the hazard ratio of fibrinogen level for disease progression. **Results:** The high fib group demonstrated poorer performance in attention, executive function, and confrontation naming than the low fib group. After adjustment for *APOE* genotype, the high fib group was associated with poor attention and executive function. After

adjustment for vascular risk factors including body mass index, hypertension, diabetes mellitus, dyslipidemia, and smoking history, the high fib group showed declined attention and confrontation naming ability. High fibrinogen levels did not predict disease progression to CDR 1. **Conclusion:** High plasma fibrinogen levels were associated with poor performance in attention in patients with MCI, regardless of *APOE* genotype or vascular risk factors.

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Introduction

Vascular pathology, neuroinflammation, and neurodegeneration are closely connected to the pathogenesis and progression of neurodegenerative disease with cognitive impairment although none of these acts as a sole cause of neurodegenerative disease [1, 2]. Vascular pathology is predominant in vascular dementia (VD), and also in Alzheimer's disease (AD), where vascular pathology and the consequent immune response are considered as a key feature of the disease pathology [3, 4].

One of the important characteristics of vascular pathology is the influx of plasma proteins into the central nervous system (CNS) through the damaged blood-brain barrier (BBB) [1]. Fibrinogen is a plasma protein that

does not exist in the CNS, and its leakage into the CNS via the BBB induces immune reactions that lead to neurodegeneration [2]. Hence, fibrinogen has been of interest as not only a marker of vascular pathology but also as an active contributor to neurodegenerative diseases such as AD, traumatic brain injury, and Parkinson's disease [2, 4, 5].

Various epidemiological studies have reported significant associations between high levels of plasma fibrinogen and impaired cognition, and fibrinogen has been shown to be a predictor for dementia [6–12]. These studies were conducted mostly in community-based populations or populations with vascular risk factors (VRFs) such as stroke, diabetes mellitus (DM), and chronic kidney disease. However, the role of fibrinogen in patients with mild cognitive impairment (MCI) deserves more attention. MCI is an early state of dementia, and the presence of BBB disruption in MCI has been demonstrated in previous studies [13]. Fibrinogen as a marker of vascular pathology could indicate specific cognitive profile patterns and predict cognitive decline in patients with MCI, which could be useful in the clinical setting.

To our knowledge, there has been only one study in an MCI population that found a significant association between high fibrinogen levels and increased risk for dementia. It had a small sample size, however, and cognitive function was assessed using the Mini-Mental State Examination (MMSE) only [14]. In this study, we aimed to investigate cognitive profiles in patients with MCI using extensive neuropsychological tests and analyze these results according to plasma fibrinogen levels in order to investigate the association between plasma fibrinogen levels and cognitive decline.

Materials and Methods

Study Population

Patients with MCI who visited the memory clinic of Seoul National University Bundang Hospital from January 2006 to June 2019 were recruited retrospectively. Patients who met the following criteria were included: (1) a diagnosis of MCI according to Petersen's criteria [15] and a Clinical Dementia Rating (CDR) scale score of 0.5 [16] and (2) plasma fibrinogen level determination at baseline evaluation.

Data Collection

All patients underwent interviews regarding current health status and past medical history, physical and neurological examination, and laboratory studies at the baseline evaluation. Demographic information including age, sex, and education was obtained at the baseline evaluation. Other information, including duration of follow-up, any follow-up cognitive assessments, the

number of patients with progression to CDR 1, time to progression to CDR 1, and final diagnoses, was also collected.

The body mass index (BMI) was calculated (weight [kg]/length [m²]). Information about VRFs such as hypertension (HTN), DM, dyslipidemia (DL), and history of smoking (categorized as current, ex-, and never smoker) was obtained. HTN was defined as previous use of antihypertensive medication, systolic blood pressure >140 mm Hg, or diastolic blood pressure >90 mm Hg. DM was defined as previous use of antidiabetic medication with the diagnosis of diabetes or a fasting blood glucose >7.0 mmol/L (>126 mg/dL). DL was defined as previous use of lipid-lowering medication or a total cholesterol >6.0 mmol/L (>240 mg/dL).

The plasma fibrinogen level was collected as a measurement of interest during the baseline evaluation and was included with routine laboratory studies in our clinic. The mean time interval of fibrinogen measurement and cognitive assessment was 19.47 ± 38.42 days. Plasma fibrinogen was measured according to clotting time (Clauss method) using STA[®]-Liquid Fib (Diagnostica Stago) and STA R MAX (Diagnostica Stago). The C-reactive protein (CRP) level was also collected to rule out acute inflammatory status, which could influence fibrinogen levels. Additionally, APOE genotype was identified by real-time PCR.

Assessment of Cognitive Function

Global cognitive status was evaluated using the MMSE [17]. Dementia severity was evaluated using the CDR Sum of Boxes (SOB) and the Global Deterioration Scale (GDS) [18]. The short form of the Geriatric Depression Scale (GDS) was used to evaluate depressive symptoms [19]. Additionally, we performed comprehensive neuropsychological tests to assess attention, verbal and visual memory, visuoconstructive function, language, and executive function. We used the Digit Span Forward and Backward tests for attention [20], the Seoul Verbal Learning Test for verbal memory [21], the Rey Complex Figure Test for visual memory and visuoconstructive function [22], the Korean version of the Boston Naming Test (BNT) for language [23], and both the categorical and phonemic fluency of the Controlled Oral Word Association Test [24] and the Stroop Colors test for executive function [25]. Raw scores from the MMSE, CDR SOB, GDS, and GDS were used for statistical analysis. The scores from the extensive neuropsychological tests were converted to standardized scores (z-scores), which were adjusted for age, sex, and education.

Statistical Analysis

Patients were divided into 2 groups according to fibrinogen level. Patients with fibrinogen levels lower than the median value of 338 mg/dL were defined as the low fibrinogen (low fib) group and those with the same or higher fibrinogen levels were defined as the high fibrinogen (high fib) group. To compare demographic, clinical, and cognitive assessment data between groups, we used the Pearson χ^2 test for categorical variables and the Student's *t* test for continuous variables.

Multiple linear regression analysis was performed to assess differences in cognitive function between groups after adjustment for APOE genotype or VRFs including BMI, HTN, DM, DL, and smoking history. Based on previous study results showing that fibrinogen is associated with an increased risk of AD and VD [8], which were also the 2 most frequent final diagnoses among subjects in our study with disease progression, we aimed to evaluate the influence of APOE genotype and VRFs on cognitive function. Additionally,

Table 1. Demographic and clinical data according to groups

	All (<i>n</i> = 643)	Low fib (<i>n</i> = 320)	High fib (<i>n</i> = 323)	<i>p</i> value
Age, years	73.6±7.6	70.9±9.0	73.6±8.0	<0.001
Female	419 (65.2)	191 (59.7)	228 (70.6)	0.004
Education, years	11.8±4.7	12.0±4.5	11.4±5.0	0.103
<i>APOE</i> ε4 ^a	168 (28.8)	89 (30.6)	79 (27.1)	0.362
Fibrinogen	348.6±67.9	296.9±29.3	399.2±61.4	<0.001
CRP	0.13±0.25	0.06±0.11	0.20±0.30	<0.001
BMI	23.1±3.2	23.2±2.9	23.5±3.2	0.312
HTN	342 (53.2)	163 (50.9)	179 (55.4)	0.269
DM	149 (23.2)	94 (29.4)	111 (34.4)	0.177
DL	205 (31.9)	30 (9.4)	29 (9.0)	0.892
Smoking history				
Current smoker	20 (3.1)	12 (3.8)	8 (2.5)	0.390
Ex-smoker	83 (12.9)	44 (13.8)	39 (12.1)	
Never smoker	540 (84.0)	264 (82.5)	276 (85.4)	
Follow-up with cognitive tests	325 (50.5)	166 (51.9)	159 (49.2)	0.528
Follow-up duration of those with cognitive test, months	58.72±35.56	56.41±35.18	60.93±35.89	0.252
Progression to CDR 1	128 (39.4)	62 (37.3)	66 (41.5)	0.496
Time to progression (CDR 1), months	41.5±31.8	43.3±30.3	39.7±33.2	0.523
Final diagnosis				
MCI	511 (79.4)	256 (80.0)	255 (78.9)	0.815
AD	104 (16.1)	49 (15.3)	55 (17.0)	
VD	12 (1.8)	6 (1.9)	6 (1.9)	
Dementia with Lewy bodies	6 (0.9)	3 (0.9)	3 (0.9)	
Frontotemporal lobe degeneration	3 (0.4)	2 (0.6)	1 (0.3)	
Corticobasal degeneration	1 (0.1)	1 (0.3)	0 (0.0)	
Idiopathic Parkinson's disease	5 (0.7)	2 (0.6)	3 (0.9)	
Progressive supranuclear palsy	1 (0.1)	1 (0.3)	0 (0.0)	

Data are presented as *n* (%) or mean ± standard deviation. BMI, body mass index; CDR, Clinical Dementia Rating; CRP, C-reactive protein; DL, dyslipidemia; DM, diabetes mellitus; HTN, hypertension; MCI, mild cognitive impairment; AD, Alzheimer's disease; VD, vascular dementia. ^a Data for 60 patients were not available.

age, sex, and education were only adjusted in the analysis of MMSE because the scores from the other neuropsychological tests had already been adjusted when converted to *z*-scores. CDR SOB and GDS scores for dementia severity and GDS scores for depressive symptoms were not adjusted for age, sex, and education.

We assessed the hazard ratios (HRs) for age, sex, education, MMSE, fibrinogen group, *APOE* genotype, BMI, HTN, DM, DL, and smoking history in the univariate Cox analysis. Follow-up duration was analyzed as a time variable and progression to CDR 1 as a status variable. The proportional assumption was examined using a log-log survival plot. Multivariate Cox regression analysis was performed to identify group differences in progression to CDR 1. Multivariate Cox analysis was implemented in 2 separate models. In the first model, *APOE* genotype was included as a covariate in addition to age, sex, education, MMSE, and fibrinogen group. In the second model, VRFs such as BMI, HTN, DM, DL, and smoking history were included as covariates in addition to age, sex, education, MMSE score, and fibrinogen group. Data were analyzed using SPSS 25 (IBM, Armonk, NY, USA), and statistical significance was set at ≤0.05.

Results

Demographic and Clinical Data of Study Population

A total of 643 patients were included in this study. The mean age of the patients was 73.6 years, and 419 (65.2%) were female. The low fib group contained 320 patients, and the high fib group contained 323 patients. Table 1 shows demographic and clinical data according to groups. The high fib group tended to be older and contained more female patients than the low fib group. The high fib group had higher levels of CRP than the low fib group although the CRP levels of both groups were in the normal range without any sign of inflammatory reaction. There were no differences in VRFs such as BMI, HTN, DM, DL, or smoking history between groups.

The mean follow-up duration of all 643 patients was 36.3 months, and there was no difference between groups.

Table 2. Cognitive assessment according to groups

	All (n = 643)	Low fib (n = 320)	High fib (n = 323)	p value
MMSE	26.0±3.2	26.2±3.2	25.8±3.2	0.177
CDR SOB	1.4±1.0	1.4±1.0	1.5±0.99	0.323
GDS	3.0±0.9	2.9±0.6	3.1±1.2	0.114
GDpS	5.8±3.9	5.7±3.8	5.9±4.0	0.458
Digit Span Forward test	-0.08±0.90	0.00±0.90	-0.17±0.89	0.017
Digit Span Backward test	-0.17±0.84	-0.09±0.85	-0.25±0.83	0.019
Korean BNT	-0.54±0.87	-0.45±0.91	-0.62±0.83	0.020
SVLT immediate recall	-0.40±0.88	-0.41±0.86	-0.39±0.90	0.741
SVLT delayed recall	-0.65±0.85	-0.68±0.84	-0.62±0.87	0.401
SVLT recognition	-0.36±0.85	-0.39±0.85	-0.34±0.85	0.481
RCFT copy	-0.35±0.87	-0.33±0.86	-0.38±0.88	0.485
RCFT delayed recall	-0.72±0.74	-0.71±0.75	-0.74±0.74	0.554
RCFT recognition	-0.34±0.94	-0.35±0.92	-0.34±0.96	0.944
Categorical fluency	-0.48±0.81	-0.42±0.82	-0.54±0.79	0.063
Phonemic fluency	-0.46±0.90	-0.41±0.85	-0.43±0.86	0.811
Stroop Colors test	-0.46±0.90	-0.36±0.93	-0.56±0.85	0.006

Data are presented as mean ± standard deviation. CDR SOB, Clinical Dementia Rating Sum of Boxes; GDS, Global Deterioration Scale; MMSE, Mini-Mental State Examination; GDpS, Geriatric Depression Scale; BNT, Boston Naming Test; RCFT, Rey Complex Figure Test; SVLT, Seoul Verbal Learning Test.

A total of 325 patients were followed up with cognitive tests. Among them, 128 patients (39.4%) progressed to CDR 1, and the mean time to progression was 41.5 months, with no difference between groups. There were also no differences between groups with regard to final diagnoses of all patients including MCI, AD, VD, dementia with Lewy bodies, frontotemporal lobe degeneration, corticobasal degeneration, idiopathic Parkinson's disease, and progressive supranuclear palsy.

Cognitive Assessment according to Groups

The cognitive assessment according to groups is shown in Table 2. The high fib group demonstrated poorer performance on the Digit Span Forward and Backward tests, BNT, and Stroop Colors test. Additionally, the high fib group showed poorer scores in the categorical fluency test although this difference was not significant. There were no differences in performance on the rest of the neuropsychological tests between groups.

Multivariate Linear Regression Analysis of Cognitive Assessment by Groups

Multivariate linear regression analysis was performed to evaluate influence of groups on cognitive function (Table 3). After adjustment for APOE genotype, the high fib group showed significantly poorer scores in the Digit

Span Backward test and the Stroop Colors test. The high fib group demonstrated poorer performance in the Digit Span Forward test and the categorical fluency test without statistical significance. After adjustment for VRFs including BMI, HTN, DM, DL, and smoking history, the high fib group presented significantly poorer scores in the Digit Span Backward test and the BNT. The high fib group showed poorer performance in the Digit Span Forward test without statistical significance.

Cox Proportional Hazard Model for Progression to CDR 1

In the univariate Cox analysis, old age, low education level, and poor MMSE performance were associated with increased risk for progression to CDR 1 with HRs (95% confidence interval [CI]) of 1.052 (1.020–1.085), 0.954 (0.921–0.988), and 0.847 (0.805–0.891), respectively (Table 4). In the multivariate Cox analysis for APOE genotype, only poor MMSE score was associated with increased risk (HR: 0.857, CI: 0.807–0.910), and in the analysis of VRFs, poor MMSE score and old age were associated with increased risk for disease progression (HR: 0.848, CI: 0.792–0.908 and HR: 1.054, CI: 1.017–1.092). Neither the univariate nor the multivariate Cox analysis of disease progression by the fibrinogen level group showed a significant association.

Table 3. Multivariate linear regression analysis of cognitive assessment by groups

Cognitive assessment	+APOE ϵ 4 B (SE), <i>p</i> value	+VRFs ^a B (SE), <i>p</i> value
MMSE ^b	0.040 (0.234), 0.863	0.019 (0.246), 0.940
CDR SOB	0.050 (0.083), 0.600	0.088 (0.088), 0.318
GDS	0.132 (0.084), 0.116	0.147 (0.090), 0.105
GDpS	0.056 (0.331), 0.866	0.067 (0.343), 0.844
Digit Span Forward test	-0.146 (0.076), 0.056	-0.141 (0.080), 0.080
Digit Span Backward test	-0.169 (0.72), 0.018	-0.152 (0.074), 0.042
Korean BNT	-0.162 (0.75), 0.310	-0.156 (0.076), 0.042
SVLT immediate recall	0.011 (0.075), 0.883	-0.034 (0.078), 0.664
SVLT delayed recall	0.054 (0.072), 0.455	0.026 (0.076), 0.729
SVLT recognition	0.029 (0.072), 0.688	0.020 (0.077), 0.800
RCFT copy	-0.062 (0.074), 0.400	0.001 (0.078), 0.990
RCFT delayed recall	-0.052 (0.064), 0.413	-0.056 (0.066), 0.394
RCFT recognition	-0.003 (0.082), 0.972	-0.011 (0.084), 0.894
Categorical fluency	-0.126 (0.069), 0.070	-0.108 (0.072), 0.134
Phonemic fluency	-0.037 (0.073), 0.608	0.000 (0.076), 0.997
Stroop Colors test	-0.197 (0.077), 0.011	-0.147 (0.078), 0.590

The dependent variable was the cognitive assessment score. The independent variable was the group (low fib vs. high fib). APOE genotype or VRFs were adjusted retrospectively. Age, sex, and education were also adjusted in the MMSE analysis. β values (SE) of the dependent variable are presented by groups. VRFs, vascular risk factors; SE, standard error; CDR SOB, Clinical Dementia Rating Sum of Boxes; GDS, Global Deterioration Scale; GDpS, Geriatric Depression Scale; BNT, Boston Naming Test; MMSE, Mini-Mental State Examination; RCFT, Rey Complex Figure Test; SVLT, Seoul Verbal Learning Test; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; DL, dyslipidemia. ^a BMI, HTN, DM, DL, and smoking history. ^b Adjusted for age, sex, and education.

Table 4. Cox proportional hazard model for progression to CDR 1 in patients with MCI

	Univariate, HR (95% CI)	Multivariate	
		APOE ϵ 4, HR (95% CI)	VRFs, ^a HR (95% CI)
Age	1.052 (1.020–1.085)*	1.025 (0.988–1.063)	1.054 (1.017–1.092)*
Female	1.177 (0.823–1.683)	0.937 (0.600–1.463)	1.351 (0.773–2.359)
Education	0.954 (0.921–0.988)*	0.992 (0.948–1.037)	1.007 (0.961–1.056)
MMSE	0.847 (0.805–0.891)*	0.857 (0.807–0.910)*	0.848 (0.792–0.908)*
Fibrinogen	1.057 (0.743–1.505)	1.082 (0.748–1.567)	0.973 (0.656–1.444)
APOE ϵ 4	0.739 (0.514–1.064)	0.777 (0.507–1.191)	NI
BMI	0.949 (0.890–1.012)	NI	0.956 (0.897–1.019)
HTN	0.792 (0.552–1.136)	NI	0.725 (0.472–1.116)
DM	1.076 (0.727–1.592)	NI	1.126 (0.729–1.739)
DL	1.051 (0.722–1.532)	NI	0.773 (0.492–1.215)
Current smoker	1.172 (0.698–1.969)	NI	1.261 (0.398–3.992)
Ex-smoker	0.990 (0.432–2.266)	NI	0.718 (0.343–1.500)
Never smoker	Reference	NI	Reference

MCI, mild cognitive impairment; CDR, Clinical Dementia Rating; HR, hazard ratio; BMI, body mass index; DL, dyslipidemia; DM, diabetes mellitus; HTN, hypertension; MMSE, Mini-Mental State Examination; NI, not included; VRFs, vascular risk factors. * $p < 0.05$. ^a BMI, HTN, DM, DL, and smoking history.

Discussion/Conclusion

In this study, we found that MCI patients with higher plasma fibrinogen levels demonstrated poor performance in attention when assessed with the Digit Span Forward and Backward tests, in executive function when tested with the Stroop Colors test, and in confrontation naming ability when assessed with the BNT. After adjustment for *APOE* genotype, higher fibrinogen level was associated with poor scores in the Digit Span Backward test and the Stroop Colors test. After adjustment for VRFs including BMI, HTN, DM, DL, and smoking history, higher fibrinogen level was associated with poor scores in the Digit Span Backward test and the BNT. However, high fibrinogen level was not related to increased risk for progression to CDR 1.

Numerous studies have shown that higher levels of fibrinogen are associated with poor performance in diverse cognitive domains including attention [26], executive function [11, 26, 27], and memory [11, 28] depending on study design and population. In longitudinal studies, higher fibrinogen levels could predict declines in global cognition [10], executive function [29], nonverbal reasoning [27, 30], and processing speed [7, 9]. Furthermore, a high fibrinogen level was related to increased risk for dementia [14], VD [8, 14, 26], and AD [8].

Fibrinogen is an intravascular protein involved in coagulation and inflammation [31]. Increased intravascular fibrinogen levels can affect plasma viscosity, platelet thrombogenesis, and red blood cell aggregation, altering vascular reactivity and damaging endothelial cell integrity [32]. The extravasation and deposition of fibrinogen into the CNS through the disrupted BBB alters the homeostasis between the vasculature and the CNS, resulting in neuroinflammation and neurodegeneration [1, 2]. Fibrinogen has a unique molecular structure with binding sites for receptors and proteins that mediate signaling for diverse processes leading to neurodegeneration in the CNS such as microglial activation, inhibition of oligodendrocyte progenitor cell differentiation and remyelination, axonal damage, binding of amyloid- β , astrocyte induction, and inhibition of neurite outgrowth [31]. Because of these effects, fibrinogen has been highlighted as a causal factor in neurological diseases with cognitive impairment [2, 3, 5, 33, 34].

In this study, the subject population with MCI was a heterogeneous group with diverse etiologies for their cognitive decline, such as amyloid and vascular pathology. Based on the results from previous studies showing that fibrinogen is a potential causative factor in AD and VD

[2], we retrospectively analyzed our MCI population after adjustment for *APOE* genotype and VRFs. After adjustment for *APOE* genotype only (not VRFs), high fibrinogen level was related to poor scores on the Digit Span Backward test and the Stroop Colors test, which are consistent with previous study results associating frontal lobe dysfunction with vascular cognitive impairment [35–37]. After adjustment for VRFs only (not *APOE* genotype/amyloid pathology), high fibrinogen level was still associated with poor performance on the Digit Span Backward test and also with poor performance on the BNT showing confrontation naming function. Confrontation naming is related to activation of the temporal lobe and hippocampus, which are vulnerable to amyloid pathology [38–40]. It is of note that a poor score in the Digit Span Backward test was associated with high fibrinogen levels after both adjustments (*APOE* genotype and VRFs). Poor attention and working memory function in the high fib group are consistent with the cognitive pattern of VD [41, 42]. This result might indicate that high levels of fibrinogen could indicate cognitive impairment associated with vascular pathology in MCI patients.

However, we could not confirm that high fibrinogen levels predict disease progression to CDR 1. This might be due to the heterogeneous characteristics of MCI patients including various pathologies with diverse disease progression patterns. A longer follow-up period or a larger number of patients might be required in order to observe the increased risk of fibrinogen level for disease progression, as a substantial number of patients (49.4%) in our study were not followed up. There were no consistent differences in cognitive profile between patients with and without follow-up (see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000510420).

There are several limitations to this study which should be mentioned. The level of fibrinogen was based on a single measurement. Although we excluded an acute inflammatory state with normal CRP levels, temporal fluctuation in plasma fibrinogen levels could be possible. Additionally, although we adjusted our data for *APOE* genotype and VRFs, other pathologic covariates could be present in addition to amyloid and vascular pathologies. Furthermore, patients with follow-up tended to be older and have more HTN and DM and poorer performance on the Digit Span test and the BNT than patients without follow-up. This could imply a selection bias, indicating that patients with more comorbidities and greater disease severity could be better followed up and included in this study. In conclusion, this study demonstrated that a high level of fibrinogen was associated with poor performance in the

attention domain in MCI patients, regardless of *APOE* genotype and VRFs. This might imply that a high fibrinogen level could indicate cognitive impairment from vascular pathology.

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Statement of Ethics

This retrospective study design was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (B-1910/568-103).

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.M. Pyun contributed to analysis and interpretation of data and writing of the manuscript. N. Ryoo and Y.H. Park contributed to revising and final approval of the manuscript. S.Y. Kim designed the study and participated in revising and final approval of the manuscript.

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