Serotonin Transporter and COMT Polymorphisms as Independent Predictors of Health-Related Quality of Life in Patients with Panic Disorder

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There is growing evidence of poor health-related quality of life (HRQOL) in patients with panic disorder (PD). However, little is known about the factors affecting HRQOL in patients with PD. The authors examined whether *5-HTTLPR* tri-allelic approach and Cathechol-O-methyltransferase (COMT) Val[158]Met polymorphism can predict HRQOL in patients with PD controlling for sociodemographic factors and disorder-related symptom levels. The sample consisted of 179 patients with PD consecutively recruited from an outpatient clinic and age- and gender ratio-matched 110 healthy controls. The SF-36 was used to assess multiple domains of HRQOL. Hierarchical multiple regression analysis was performed to determine the independent effect of the *5-HTTLPR* and *COMT* Val[158]Met on the SF-36 in panic patients. Patients with PD showed lowered HRQOL in all sub-domains of the SF-36 compared to healthy controls. The *5-HTTLPR* independently and additively accounted for 2.2% of variation (6.7% of inherited variance) of perceived general health and the *COMT* Val[158]Met independently and additively accounted for 1.5% of variation (5.0% of inherited variance) of role limitation due to emotional problems in patient group. The present study suggests that specific genetic polymorphisms are associated with certain domains of HRQOL and provides a new insight on exploring the factors that predict HRQOL in patients with PD.

Keywords: Quality of Life; Panic Disorder; *5-HTTLPR*; *COMT* Val[158]Met

INTRODUCTION

Panic disorder (PD) is a common chronic condition associated with significant social morbidity and increased health care utilization (1,2). There is growing evidence that poor health-related quality of life (HRQOL) is noted in patients with PD (3-5) even in remission state (6). However, little is known about the factors that affect HRQOL of panic patients. Although several demographic, illness-specific symptom severity, psychiatric morbidity, and social support factors were reported to predict HRQOL in panic patients (3,4,7-9), the variance of the explanation is quite small to modest. Thus, it raises the question regarding other factors that affect the HRQOL. Conceptually, QOL is defined as the subjective as well as objective evaluation of physical and mental status, well-being, and environmental factors (10). A recent twin study showed that genetic factors accounted for 17% to 33% of the variance of the HRQOL by the 36-item Short-Form Health Survey (SF-36) (11), a reliable and widely

used QOL-related research tool (12,13). However, it is unknown which specific genes affect HRQOL in patients with PD.

Serotonin transporter gene linked polymorphism (*5-HTTLPR*) and Catechol-*O*-methyltransferase (*COMT*) Val[158]Met polymorphism have been extensively studied in psychiatric research field and known to be closely related to anxiety disorders including PD (14-17). Lesch et al. (17) first reported that individuals with one or two copies of short (S) alleles of the *5-HTTLPR* have less efficient transcription of the 5-HTT gene compared to those with homozygous long (L) alleles (L/L) and show higher levels of anxiety-related trait. However, studies on the role of *5-HTTLPR* have been inconsistent (18-20). Recently, several researcher groups revealed that there exists a single nucleotide polymorphism within the L allele that can be further divided into L$_A$ (A variant) or L$_G$ (G variant) (21-23). The former is known to yield high 5-HTT mRNA levels and L$_G$ is functionally equivalent to the low-mRNA-expressing S allele. This tri-allelic (S or L$_G$ vs. L$_A$) approach has opened new opportunities for exploring

the role of *5-HTTLPR* in psychiatric researches (21,24,25). In the present study, S or L_G allele was designated as S′ whereas L_A allele as L′.

COMT is a major enzyme that metabolizes catecholamines including dopamine and norepinephrine and the enzymatic activity exhibits allelic variation according to the genetic locus *COMT* Val[158]Met (26,27). *COMT* Val allele encodes for valine, associated with high activity whereas the Met allele encodes for methionine at position 108/158. Research has shown that *COMT* Val[158]Met is associated with panic disorder (15).

Thus, the present study was to examine whether *5-HTTLPR* and *COMT* Val[158]Met could be independent predictors of HRQOL in patients with PD controlling for sociodemographic data and illness-related symptomatology.

MATERIALS AND METHODS

Participants

The sample consisted of 179 panic patients with or without agoraphobia who met the diagnostic criteria in the Structured Clinical Interview for DSM-IV (SCID-IV) (28) by experienced psychiatrists. They were recruited consecutively at the Department of Psychiatry of CHA Bundang Medical Center. Age- and gender ratio-matched 110 healthy controls were recruited by local advertisement and referrals. All subjects were 18 to 70 years old, unrelated, and of Korean ancestry. Exclusion criteria included any history of schizophrenia, bipolar disorder, alcohol and substance abuse or dependence, mental retardation, and current or past serious medical or neurological disorders.

Measures

The SF-36 (12,29) was used to determine HRQOL in patients with PD. It consists of eight subscales: physical functioning (the ability to perform a range of physical activities), role physical (the impact of physical health on usual role activities), bodily pain, general health (overall perception of personal health), vitality (energy and fatigue), social functioning (interference of physical and emotional problems in social activities), role emotional (impact of emotional problems on usual role activities), and mental health (psychological distress and well-being). The raw scores of SF-36 were transformed to a 0 to 100 range with higher scores indicating better HRQOL. The Panic Disorder Severity Scale (PDSS) (30) was used to assess the overall panic-related symptoms. Depressive symptoms were determined by the Beck Depression Inventory (BDI) (31).

Genotyping

Genomic DNA was extracted from blood (stored frozen) using a G-DEXTM II Genomic DNA Extraction Kit (Intron Biotechnology, Seongnam, Korea). The genotyping was based upon analysis of primer extension products generated from previously am-

plified genomic DNA using a chip-based matrix assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry platform (Sequenom, San Diego, CA, USA). Genotyping for the triallelic *5-HTTLPR* was performed as previously described method (32) with slight modification. Traditional biallelic polymerase chain reaction (PCR) analysis yields an "S" 486 bp and an "L" 529 bp fragment. MSPI restriction enzyme digestion analysis were also performed and resulted in the following fragments: 340, 127, and 62 bp for the L_A allele, 297, 127, and 62 bp for the S_A allele, 174, 166, 127, and 62 bp for the L_G allele and 166, 131, 127, and 62 bp for the S_G allele. The *COMT* Val[158]Met was analyzed as previously described method (16).

Statistical analysis

Pearson correlation coefficients measured the linear relationship between the SF-36 subscales and age, education level, duration of illness, and clinical data. For binary measures, Student's *t*-test was used to compare mean scores of the SF-36. For categorical variables with more than 2 levels, one-way analysis of variance (ANOVA) was used to compare the SF-36 scores. Hardy-Weinberg equilibrium was tested using χ^2 test. The Bonferroni correction was applied for the multiple tests according to the two genetic polymorphisms. Hierarchical multiple regression analysis was performed to examine whether *5-HTTLPR* or *COMT* Val[158]Met could independently predict the subscales of SF-36 controlling for age, gender, and other variables that were statistically significant in bivariate analysis. Tests were two-tailed and alpha was set at 0.05. Data analysis was conducted by using SPSS version 20 software (SPSS, Inc., Chicago, IL, USA).

Ethics statement

All study procedures complied with CHA Bundang Medical Center institutional review board regulations (IRB number: 2011-164) and Declaration of Helsinki. After a complete description of the study was given to the subjects, written informed consent was obtained.

RESULTS

Table 1 displays sociodemographic and clinical features of the sample. Of the 179 patients with PD, 96 (53.6%) were female, with a mean age of 39.1 years (SD = 10.6), a mean education of 12.9 years (SD = 2.9). One-hundred seven patients (65.4%) were diagnosed as PD with agoraphobia. Patients with PD showed lowered HRQOL in all sub-domains of the SF-36 compared to healthy controls. Panic patients were less educated and had less amount of monthly income. More divorced/separated/widowed subjects were in patient group. Subjects in unemployed states were more in patient group than in normal control group.

In patients with PD, male gender was related with better function in terms of physical functioning, bodily pain, and vitality.

Table 1. Demographic and clinical characteristics of study subjects

Variables	Patients (n = 179)	Controls (n = 110)	t/F/χ^2	P
Age, mean (SD), yr	39.1 (10.6)	38.1 (11.0)	0.64	0.426
Education	12.9 (2.90)	15.6 (2.69)	63.3	< 0.001
Duration of illness, mean (SD), mon	42.1 (67.1)	-	-	-
Gender, n (%)			0.02	0.880
Male	83 (46.4)	50 (45.4)		
Female	96 (53.6)	60 (54.5)		
Job, n (%)			18.2	< 0.001
Employed	111 (62.0)	94 (85.5)		
Unemployed	68 (38.0)	16 (14.5)		
Monthly household income, n (%)			15.8	< 0.001
< $2,000	26 (14.5)	7 (6.4)		
$2,000-$5,000	106 (59.2)	50 (45.5)		
≥ $5,000	47 (26.3)	53 (48.1)		
Marriage, n (%)			7.21	0.027
Married	121 (67.6)	65 (59.1)		
Never married	43 (24.0)	41 (37.3)		
Divorced/separated/widowed	15 (8.4)	4 (3.6)		
With agoraphobia, n (%)	117 (65.4)	-	-	-
PDSS, mean (SD)	9.6 (6.6)	-	-	-
BDI, mean (SD)	17.8 (12.1)	-	-	-
SF-36, mean (SD)				
Physical functioning	71.6 (18.5)	86.5 (12.0)	55.6	< 0.001
Role physical	60.1 (30.1)	83.9 (18.7)	55.6	< 0.001
Bodily pain	49.9 (30.2)	87.0 (16.1)	141.2	< 0.001
General health	39.1 (20.0)	65.6 (15.3)	142.0	< 0.001
Vitality	39.4 (22.0)	63.1 (15.1)	99.7	< 0.001
Social functioning	59.3 (25.7)	86.9 (16.0)	101.7	< 0.001
Role emotional	60.0 (30.8)	86.7 (18.5)	67.5	< 0.001
Mental health	49.2 (20.5)	73.2 (13.4)	118.6	< 0.001

PDSS, Panic Disorder Severity Scale; BDI, Beck Depression Inventory; SF-36, 36-Item Short Form Health Survey.

Age was positively correlated with the vitality, role-emotional, and mental health. Education was associated with better QOL of physical functioning, role-physical, and bodily pain. Employment status was associated with better QOL in all subscales of the SF-36 except for role-physical and role-emotional. Patients with higher monthly income reported better QOL except for mental health. Married patients reported better role-physical, vitality, social functioning, role-emotional, and mental health compared to those who had never married. Both the PDSS and BDI were negatively correlated with all domains of the SF-36 (Table 2).

The genotype frequencies in the *5-HTTLPR* and *COMT* Val[158] Met in patient group were in Hardy-Weinberg equilibrium (S'S' = 129 [72.1%]; S'L' = 46 [25.7%]; L'L' = 4 [2.2%], *P* = 1.0 and Val/Val = 94 [52.5%]; Met/Val = 73[40.8%]; Met/Met = 12 [6.7%], *P* = 0.91). Panic patients with *5-HTTLPR* S'S' showed a trend to be associated with poorer general health (corrected *P* = 0.076) compared to L' carriers. Patients with *COMT* Val/Val were significantly associated with poor role-emotional (corrected *P* = 0.032) (Table 2). In hierarchical multiple regression analysis, *5-HTTLPR* S'S' predicted poor general health (ΔR^2 = 0.022, *P* = 0.018). *COMT* Val/Val also predicted poor role-emotional (ΔR^2 = 0.015, *P* = 0.048) controlling for sociodemographic factors and disorder-related symptom levels (Table 3).

DISCUSSION

Patients with PD showed lowered HRQOL in all sub-domains of the SF-36 compared to healthy controls which is largely consistent with previous reports (3-5). In patient group, the tri-allelic approach of *5-HTTLPR* independently and additively accounts for 2.2% of variation (6.7% of inherited variance) of general health (i.e. S'S' with poor HRQOL). The *COMT* Val[158]Met independently and additively accounts for 1.5% of variation (5.0% of inherited variance) of role-emotional (i.e., *COMT* Val/Val with poor HRQOL). To our knowledge, this is the first study to examine the independent effect of specific genetic polymorphisms on the HRQOL in patients with PD. In our data, socioeconomic variables accounted for 7%-20% of each domains of the SF-36. Disorder-related symptom levels in terms of PDSS and BDI scores explained 10%-25% additionally which is largely consistent with previous results (3,7).

The implications of the *5-HTTLPR* in panic disorder have been inconsistent. Kim et al. (33) reported no association between the *5-HTTLPR* and PD in a Korean sample. Recent data of ours also suggest that even tri-allelic approach shows no direct association between the *5-HTTLPR* and PD in a Korean sample (34). Taken together, the present study suggests that the *5-HTTLPR* is related with specific domains (i.e., perception of

Table 2-1. Factors associated with health-related quality of life in patients with panic disorder

Factors	Physical functioning		Role physical		Bodily pain		General health	
Continuous variables	r	P	r	P	r	P	r	P
Age	0.081	0.278	0.135	0.071	0.044	0.556	-0.012	0.873
Education	0.215	0.004	0.193	0.010	0.254	0.001	0.125	0.095
Length of illness	-0.106	0.159	0.032	0.675	-0.046	0.540	-0.070	0.348
PDSS	-0.387	< 0.001	-0.414	< 0.001	-0.470	< 0.001	-0.429	< 0.001
BDI	-0.420	< 0.001	-0.417	< 0.001	-0.420	< 0.001	-0.503	< 0.001
Dichotomous variables	Mean (SD)	t or F	P	Mean (SD)	t or F	P	Mean (SD)	t or F	P	Mean (SD)	t or F	P
Gender		2.316	0.022		0.545	0.586		2.709	0.007		0.838	0.403
Male	75.1 (19.1)			61.4 (31.0)			56.4 (27.8)			40.5 (20.2)		
Female	68.7 (17.6)			59.0 (29.4)			44.3 (31.1)			38.0 (19.8)		
Job		2.722	0.007		1.159	0.248		2.680	0.008		2.470	0.014
Employed	74.5 (18.1)			62.2 (29.3)			54.6 (29.3)			42.0 (20.4)		
Unemployed	66.9 (18.4)			56.8 (31.2)			42.3 (30.2)			34.5 (18.6)		
Monthly household income		7.645	0.001		7.376	0.001		7.823	0.001		4.108	0.018
< $2,000	59.6 (21.4)			41.3 (28.0)			32.5 (29.1)			30.4 (20.4)		
$2,000-$5,000	75.5 (16.5)			61.1 (29.2)			49.5 (29.3)			39.1 (20.5)		
≥ $5,000	76.4 (18.9)			68.4 (29.3)			60.5 (28.5)			44.1 (17.1)		
Marriage		0.222	0.801		3.440	0.034		2.371	0.096		0.240	0.787
Married	72.2 (18.2)			64.1 (28.2)			53.3 (30.8)			39.8 (20.5)		
Never married	70.0 (19.3)			50.9 (31.4)			42.4 (26.0)			37.3 (17.1)		
Divorced/separated/widowed	72.0 (18.5)			54.6 (35.6)			44.4 (32.8)			39.0 (24.0)		
5-HTTLPR*		-1.238	0.434		-1.248	0.428		-1.132	0.518		-2.001	0.076
S'S'	70.6 (19.0)			58.4 (30.5)			48.3 (31.0)			37.2 (19.2)		
L' carrier	74.4 (17.2)			64.6 (28.8)			54.0 (27.6)			44.1 (21.2)		
COMT Val[158]Met*		-2.328	0.042		-1.224	0.446		-1.619	0.214		-0.176	1.000
Val/Val	68.6 (17.9)			57.5 (29.1)			46.5 (30.9)			38.9 (19.8)		
Met carrier	75.0 (18.7)			63.0 (31.1)			53.7 (29.0)			39.4 (20.3)		

PDSS, Panic Disorder Severity Scale; BDI, Beck Depression Inventory.
*The Bonferroni correction was applied for the multiple tests according to the two genetic polymorphisms.

Table 2-2. Factors associated with health-related quality of life in patients with panic disorder

Factors	Vitality		Social functioning		Role emotional		Mental health	
Continuous variables	r	P	r	P	r	P	r	P
Age	0.179	0.016	0.140	0.062	0.206	0.006	0.214	0.004
Education	0.076	0.311	0.122	0.103	0.083	0.271	0.024	0.750
Length of illness	-0.035	0.644	0.100	0.182	0.090	0.233	0.074	0.327
PDSS	-0.463	< 0.001	-0.551	< 0.001	-0.427	< 0.001	-0.586	< 0.001
BDI	-0.531	< 0.001	-0.509	< 0.001	-0.517	< 0.001	-0.645	< 0.001
Dichotomous variables	Mean (SD)	t or F	P	Mean (SD)	t or F	P	Mean (SD)	t or F	P	Mean (SD)	t or F	P
Gender		2.510	0.013		1.634	0.104		0.193	0.847		1.485	0.139
Male	43.8 (21.8)			62.7 (23.9)			60.4 (30.2)			51.7 (19.1)		
Female	35.6 (21.5)			56.4 (27.0)			59.5 (31.5)			47.1 (21.6)		
Job		3.360	0.001		2.156	0.032		1.137	0.257		2.901	0.004
Employed	43.6 (21.7)			62.5 (24.2)			62.0 (30.1)			52.7 (18.6)		
Unemployed	32.5 (20.8)			54.0 (27.4)			56.6 (32.0)			43.7 (22.4)		
Monthly household income		4.218	0.016		4.850	0.009		7.549	0.001		2.979	0.053
< $2,000	28.1 (18.7)			45.7 (27.4)			40.7 (29.6)			42.5 (15.6)		
$2,000-$5,000	40.9 (20.5)			60.4 (23.8)			60.8 (28.6)			48.6 (19.7)		
≥ $5,000	42.3 (25.1)			64.4 (27.0)			68.8 (32.3)			54.4 (23.7)		
Marriage		4.381	0.014		3.125	0.046		8.639	< 0.001		4.057	0.019
Married	41.8 (23.0)			61.8 (24.6)			66.2 (27.7)			51.5 (21.0)		
Never married	31.0 (18.8)			50.9 (27.5)			45.0 (30.5)			41.6 (19.4)		
Divorced/separated/widowed	43.8 (14.9)			36.3 (26.1)			52.8 (40.3)			52.7 (14.0)		
5-HTTLPR*		-0.233	1.000		-0.149	1.000		-0.190	1.000		0.493	1.000
S'S'	39.1 (21.8)			59.1 (25.2)			59.7 (31.4)			49.7 (19.1)		
L' carrier	40.0 (22.6)			59.8 (27.4)			60.7 (29.7)			47.9 (24.0)		
COMT Val[158]Met*		-0.995	0.642		-1.447	0.300		-2.434	0.032		-1.867	0.128
Val/Val	37.8 (22.1)			56.6 (23.5)			54.7 (30.4)			46.5 (19.7)		
Met carrier	41.1 (21.8)			62.2 (27.9)			65.8 (30.4)			52.2 (21.1)		

PDSS, Panic Disorder Severity Scale; BDI, Beck Depression Inventory.
*The Bonferroni correction was applied for the multiple tests according to the two genetic polymorphisms.

Table 3. Hierarchical multiple regression analysis of factors associated with quality of life in panic disorder patients

Risk factors	Dependent variables											
	General health						Role-emotional					
Predictors	β	t	P	R²	ΔR²	P	β	t	P	R²	ΔR²	P
Step 1				0.070		0.027				0.165		< 0.001
Age	0.017	0.236	0.814				0.117	1.336	0.183			
Gender (reference: male)	0.043	0.518	0.605				-0.009	-0.125	0.900			
Job (reference: employment)	-0.179	-2.112	0.036									
Monthly household income (reference: < $2,000)												
$2,000-$5,000	0.214	2.015	0.045				0.315	3.060	0.003			
≥ $5,000	0.275	2.577	0.011				0.382	3.691	< 0.001			
Marriage (reference: Divorced/ separated/widowed)												
Married							0.135	1.078	0.283			
Never married							-0.096	-0.685	0.494			
Step 2*				0.313	0.243	< 0.001				0.347	0.182	< 0.001
PDSS	-0.207	-2.396	0.018				-0.114	-1.342	0.181			
BDI	-0.359	-4.235	< 0.001				-0.378	-4.496	< 0.001			
Step 3†				0.335	0.022	< 0.001				0.362	0.015	< 0.001
5-HTTLPR S'S' (reference: L' carrier)	-0.151	-2.382	0.018									
COMT Val/Val (reference: Met carrier)							-0.125	-1.991	0.048			

PDSS, Panic Disorder Severity Scale; BDI, Beck Depression Inventory.
*Step 2 includes variables in step 1; †Step 3 includes variables in step 2.

general health) of HRQOL rather than with psychopathology or symptoms in patients with PD. The COMT Val[158]Met was not associated with the symptomatology in terms of PDSS and BDI. Thus, the COMT Val[158]Met is also related with specific domain of HRQOL in terms of the SF-36 (i.e., role-emotional) rather than with symptoms in patients with PD. This is consistent with previous studies showing that the HRQOL is another different domain compared to symptoms in panic disorder (4).

Interestingly, our finding suggests that different domains of HRQOL in terms of the SF-36 have a different genetic basis. It is well known that the 5-HTTLPR is closely related with 5-HT neurotransmitter system and the COMT Val[158]Met with dopamine and norepinephrine system (17,26,27). Specifically, our finding means that increased serotonergic neurotransmission is associated with poor HRQOL in terms of general health while decreased catecholaminergic neurotransmission is associated with more role limitation due to emotional problems. Given that the magnitude of variance of the two genetic polymorphisms in our study was much smaller than proposed total variation of inheritance of the SF-36 (11), it is also plausible that there should be other genes that explain the rest of the variance in general health and role-emotional in patients with PD. On the other hand, it is also possible that there exist other genetic polymorphisms rather than 5-HTTLPR and COMT Val[158]Met that explain other domains of the SF-36.

Ethnicity and culture are important factors that should be considered. Although little is known about the ethnic or cultural effects on the profile of SF-36 in patients with PD, studies of other conditions suggest the possibility of different profile of

the domains of SF-36 by different ethnicity or cultures (35,36). The previous studies (33,37) showed that the distribution as well as the roles of both 5-HTTLPR and COMT Val[158]Met in Korean panic patients are different from those in Westerners. However, in terms of the COMT Val[158]Met, we recently found that the frequency of COMT Val/Val is higher in the panic patient group than in normal controls (unpublished data, available at request), consistent with the results in Caucasians and contrary to the report by Woo et al. (37). Thus, further studies in other ethnic groups or cultures are warranted.

The present study has several limitations. First, our investigation about the relationship between the genetic factors and HRQOL was performed only in panic patients, not in healthy controls or other psychiatric illnesses. Thus, it is unclear whether the relationship between the 5-HTTLPR and COMT Val[158]Met and HRQOL in terms of the SF-36 is specific to PD. Second, our sample size was too small to examine the effect of the 5-HTTLPR L' or COMT Met homozygotes on HRQOL. It is known that the frequencies of L or L' allele as well as COMT Met allele in Asians (especially, in Korean and Japanese populations) are much less compared to those in Westerners (15,22,33). Third, we used the data reported by Romeis et al. (11) in which the subjects were middle-age, middle-class Caucasians, to calculate the portion of the genetic effect in terms of inheritance of the SF-36. Finally, the significant differences in education level and job status might have played as confounding factors for explaining the between group difference in HRQOL. Further studies on the heritability of SF-36 in patients with PD as well as in Asians are needed for more accurate calculation of the propor-

tion of variance in terms of inheritance by certain genetic polymorphisms.

In conclusion, the present study suggests that the *5-HTTLPR* S'S' independently predicts poor perceived general health (2.2% of total variation and 6.7% of variance in terms of inheritance) and *COMT* Val/Val are related with poor functioning in role-emotional (1.5% of total variation and 5.0% of variance in terms of inheritance) in terms of the SF-36 controlling for sociodemographic factors and disorder-related symptom levels in patients with PD. Our finding also shows that specific domains of the SF-36 are associated with the specific genetic polymorphisms that are closely related with specific neurotransmitter systems. In addition, the finding that the magnitude of explanation for HRQOL by symptom levels is not so large is consistent with the previous reports and suggests the need to include HRQOL in assessment of the patients. Finally, the total variance of prediction by sociodemographic factors, disorder-related symptoms, and the two genetic polymorphisms were all less than 40%, which warrants exploration of other factors that explain the HRQOL in patients with PD.

DISCLOSURE

AUTHOR CONTRIBUTION

Conception and design: Choe AY, Kim BR, Lee JY, Choi TK, Lee SH. Acquisition of data: Choe AY, Kim BR, Choi TK, Lee SH. Analysis and interpretation of data: Kang EH, Choe AY, Kim BR. First writing of manuscript: Kang EH, Choe AY. Revision of the manuscript: Kang EH, Choe AY, Na HR, Lee SH. Agree with the manuscript contents and conclusions: all authors.

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