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Differences in clinical features between focal and extensive types of cystitis glandularis in patients without a previous history of urinary tract malignancy

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Purpose: To understand the clinical differences of cystitis glandularis (CG), a proliferative disorder of urinary bladder epithelium, based on the extent of cystoscopic findings in patients without a history of urinary tract malignancy.

Materials and Methods: We conducted a review of patients diagnosed with CG in two tertiary hospitals from 2005 to 2021. Patients with previous or concurrent history of urinary tract malignancy were excluded. Medical records, including demographics, endoscopic and all available imaging studies, and managements, were reviewed. Patients were divided into two types according to extent of the lesion, and their clinical features were compared.

Results: In total, 110 patients were enrolled in the final analysis, with 36 (32.7%) classified as extensive type and 74 (67.3%) as focal type. Patients with extensive type were predominantly males and relatively younger than those with focal type (p=0.025). Voiding problems were more strongly associated and hydronephrosis caused by CG was significantly more common in the extensive type (p=0.005 and p=0.003, respectively). Multiple transurethral resection procedures were more frequently performed in the extensive type (p=0.017). Subsequent urinary tract malignancy was observed in four patients, all of whom had focal-type CG.

Conclusions: There were significant differences in clinical features between the extensive- and focal-types CG. The extensive type was more often associated with urologic complications. Meanwhile, in the focal type, subsequent urinary tract malignancy might develop during the follow-up period. Thus, thorough initial work-up and careful follow-up is necessary despite the benign nature of CG. Annual surveillance cystoscopy may be appropriate.

Keywords: Carcinoma, transitional cell; Follow-up studies; Hydronephrosis; Urinary bladder neoplasms; Urologic diseases

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INTRODUCTION

Cystitis glandularis (CG) is a proliferative disorder of the mucus-producing glands within the mucosa and submucosa of the urinary bladder epithelium, which is characterized by glandular metaplasia of the transitional cells [1]. CG with intestinal type, also called intestinal metaplasia, occurs when the bladder epithelium acquires intestinal-type goblet cells interspersed among the columnar cells, morphologically resembling colonic mucosa [2]. While CG was previously considered a premalignant condition of bladder adenocarcinoma, case series studies have found no evidence that it increases the risk of subsequent malignancy [3-5]. Although CG is often seen in association with carcinoma, it is likely to represent a reactive condition, possibly secondary to inflammation associated with carcinoma, rather than a premalignant condition [2]. CG typically presents with irregular or nodular lesions with a cobblestone pattern on cystoscopy but may develop into a papillary or polypoid mass, which mimics carcinoma [6]. Thus, a biopsy or resection of the lesion is necessary for a definitive diagnosis as a malignant tumor cannot be ruled out with only cystoscopic findings or imaging studies [7].

The clinical course of CG varies for each patient. It can present as an incidental bladder tumor but is also associated with clinically significant urologic conditions, such as hematuria, flank pain, urinary stone, and urinary obstruction [8]. Several reports demonstrated obstructive uropathy requiring urological interventions, including transurethral resection (TUR), ureteral stent insertion, percutaneous nephrostomy, and cystectomy with urinary diversion [7-19]. Meanwhile, the extent of CG can range from focal to diffuse/extensive, and severe cases requiring aggressive management are typically associated with diffuse and extensive lesions [15-17].

Despite its benign nature, extensive types of CG can be associated with significant urologic conditions. However, the difference in clinical features between focal- and extensive-types of CG has not yet been studied. Therefore, the aim of this study was to investigate the clinical features of CG based on the disease extent of cystoscopic findings in patients, without a history of urinary tract malignancy.

MATERIALS AND METHODS

1. Study population

We reviewed the electronic medical records of all patients with pathologically proven CG in two tertiary hospitals from January 2005 to December 2021. The Severance Clinical Research Analysis Portal service of the Severance Hospital was used to collect the research data. Patients with a previous or concurrent history of urinary tract malignancy were excluded to elucidate the clinical features of CG more clearly. A total of 169 consecutive patients, who were pathologically diagnosed with CG during the study period, were identified. Of them, 59 patients with a previous or concurrent history of urinary tract malignancy were excluded. Finally, 110 patients were enrolled in the analysis, with a median follow-up duration of 3.3 years (range: from 7 days to 15.2 years).

2. Data collection and classification of cystitis glandularis

Patients' clinical and pathological features and follow-up information were retrieved from the database. Patient demographics and medical history, such as age at diagnosis, sex, hypertension, diabetes mellitus, smoking status, and body mass index, were collected. Clinical presentation was evaluated based on the records of the initial visit and categorized into voiding problems, gross hematuria, flank pain, microscopic hematuria, and incidental findings on imaging studies.

Patients underwent TUR of the bladder, and the presence of CG was pathologically confirmed. Pathological information, such as concomitant intestinal metaplasia or other relevant findings, were obtained. Based on cystoscopic findings, the location and extent of CG were determined via independent review by two urologists (J.J. and J.S.H.). They tried to reach a consensus, and any disagreement was discussed with a third author (K.S.C.). The extent of CG was classified into either focal or extensive types. Focal type was defined as a tumor showing relatively small, nodular, and focal features, while extensive type was defined as tumors showing relatively large, multinodular, and extensive features. The extensive-type CG was usually circumferentially involved around the bladder neck and trigone area (Fig. 1). All available imaging studies, such as ultrasonography, computed tomography, and magnetic resonance imaging, were reviewed, and detailed treatment and follow-up information was also obtained.

3. Statistical analysis

Categorical variables were evaluated using chi-square test, and continuous variables were evaluated using independent samples t-test to identify between focal- and extensive-types of CG. All reported p-values were two-sided, and statistical significance was set at $p<0.05$. Statistical analyses were performed using software programs (SAS® System for Windows®, version 9.4 [SAS Institute Inc., Cary, NC, USA]).

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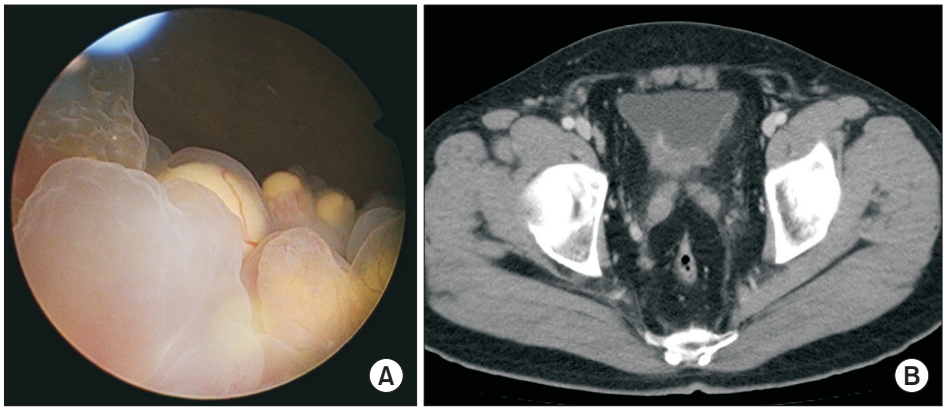

Fig. 1. Typical findings of extensive-type cystitis glandularis on cystoscopy and computed tomography. (A) Cystoscopic view of pathologically confirmed cystitis glandularis. (B) Computed tomography showing a diffuse wall thickening of posterior wall.

4. Ethics statement

This study was performed in accordance with all applicable laws and regulations, good clinical practices, and ethical principles, as described in the Declaration of Helsinki. The Institutional Review Board of the Gangnam Severance Hospital approved the study protocol (approval number: 3-2022-0268). Written informed consent was waived due to the retrospective nature of the study.

RESULTS

The mean age of the patients was 52 years, ranging from 20 to 86 years, and the male-to-female ratio was 2.4:1. Among patients with CG, 32 (30.2%) had a history of hypertension, and 9 (8.5%) had diabetes mellitus. Forty-seven patients (44.3%) were current or ex-smokers. Presenting symptoms were gross hematuria, voiding problems, and flank pain in 43.6%, 27.3%, and 10.9% of the patients, respectively. Asymptomatic patients accounted for 30% of the cases. Presentation of CG in these patients was microscopic hematuria or incidental findings on imaging studies during health check-up or work-up for other medical conditions (Table 1).

According to cystoscopic findings, the trigonal area (n=87, 79.1%) was the most common site of CG. Imaging studies revealed urinary stones in 21 patients (22.3%), and hydronephrosis was found in 16 patients (17.0%). Among the 16 patients with hydronephrosis, 6 had hydronephrosis caused by CG itself, while urinary stones and ureteral strictures accounted for hydronephrosis in the remaining 10 patients (Table 1).

Thirty-six patients (32.7%) had the extensive-type CG, and 74 (67.3%) had the focal type. Patients with the extensive type were predominantly males (97.2%) and relatively younger than those with the focal type (40.4 y vs. 57.1 y, p=0.025). Most females with CG had the focal type, and only one female had the extensive-type CG. Cigarette smoking was more frequently related to the extensive type (60.0% vs. 36.6%, p=0.023). Patients with the focal type had a higher incidence of hypertension, but the incidence of diabetes mellitus was not significantly different between the two types. Gross hematuria was more commonly reported in the focal type (51.4% vs. 27.8%, p=0.019), whereas voiding problems were more frequently associated with the extensive type (44.4% vs. 18.9%, p=0.005). There was no difference in the incidence of concomitant urinary stones and hydronephrosis between the two types, but hydronephrosis caused by CG itself was significantly more common in the extensive type (83.3% vs. 10.0%, p=0.003) (Tables 2, 3). Thirteen patients (11.8%) were treated with additional TUR at the physician's discretion. Multiple TUR procedures were more frequently performed in the extensive type (26.5% vs. 7.7%, p=0.017). Intestinal metaplasia was more commonly observed in the extensive type than in the focal type (16.7% vs. 4.1%, p=0.024) (Table 2).

Subsequent diagnoses of urinary tract malignancy were made in four patients with focal-type CG (Table 4), but there was no difference in the occurrence of subsequent urinary tract malignancy between the two types. All cases of urinary tract malignancy were urothelial carcinoma, and no adenocarcinoma was observed (Tables 1, 2).

DISCUSSION

Since the early 1900s, CG have been considered as a premalignant lesion of adenocarcinoma [20]. The first observation of concomitant presence of CG and adenocarcinoma of the bladder was reported in 1950, implicating that adenocarcinoma developed from CG [21]. In 1980, the first case was reported of adenocarcinoma of the urinary bladder in a patient with pelvic lipomatosis and CG, advocating for endoscopic follow-up of patients with pelvic lipomatosis [22]. Sporadic case reports have supported the relationship

Table 1. Baseline characteristics of patients with CG without previous history of urinary tract malignancy

Variable	Value
Age (y)	52 (20–86)
Sex	
Female	32 (29.1)
Male	78 (70.9)
Hypertension	32 (30.2)
Diabetes mellitus	9 (8.5)
Smoking history	47 (44.3)
Body mass index (kg/m^2)	24.4 (14.9–35.8)
Clinical presentation	
Gross hematuria	48 (43.6)
Voiding problem	30 (27.3)
Flank pain	12 (10.9)
Incidental tumor on images	26 (23.6)
Microscopic hematuria	7 (6.4)
Location	
Trigone	87 (79.1)
Posterior wall	6 (5.4)
Dome	4 (3.6)
Lateral wall	4 (3.6)
Anterior wall	2 (1.8)
Urethra	2 (1.8)
Unknown	5 (4.5)
Extent	
Focal	74 (67.3)
Extensive	36 (32.7)
Urinary stone	21 (22.3)
Kidney	14 (66.7)
Ureter	6 (28.6)
Bladder	5 (23.8)
Hydronephrosis	16 (17.0)
Hydronephrosis caused by CG	6 (6.4)
Concomitant intestinal metaplasia	9 (8.2)
Subsequent diagnosis of cancer	4 (3.6)

Values are presented as mean (range) or number (%).
CG, cystitis glandularis.

between pelvic lipomatosis, CG, and further adenocarcinoma of the bladder [23,24]. However, several case series studies have revealed that there is no evidence that CG increases the future risk of malignancy, and none of their patients were associated with pelvic lipomatosis, therefore, one of the authors concluded that surveillance cystoscopy was not recommended [3-5]. This study also supports that CG is no longer considered a precursor of bladder adenocarcinoma, and no pelvic lipomatosis was found. Like in other case series studies, intestinal metaplasia was not a strong risk factor of bladder adenocarcinoma (Table 5). Although intestinal metaplasia was more common in the extensive-type CG, there was no subsequent adenocarcinoma during the follow-up period in both types. However, subsequent urothelial carcinoma was found in four patients, which may have been missed on initial examination or occurred later. As described in Table 4, all of these patients were males, had the focal type, and were relatively older. The interval of diagnosis from CG to cancer was 6, 12, 17, and 36 months. Therefore, thorough initial work-up and careful follow-up is necessary despite the benign nature of CG, especially in patients with the focal type.

To the best of our knowledge, this study is the first to analyze the clinical features of focal- and extensive-types CG in patients. Briefly, CG was more common in males, and the extensive type was overwhelmingly male-dominant, and had a high proportion of smokers. It is unclear whether the pathogenesis of CG is related to the male sex itself or to the high smoking rate in males. In contrast, the younger age of onset in the extensive type suggests the possible involvement of internal genetic factors rather than smoking history. Hypertension was less common in patients with the extensive type, which might be associated with their significantly younger age compared to those with the focal type. Diabetes mellitus showed a similar tendency but did not reach statistical significance. Patients with the extensive type had a relatively higher incidence of voiding problems or hydronephrosis, which can be explained by the trigonal location and large size of the lesion.

Although differences in the incidence of CG according to sex have not yet been demonstrated [25], this study indicates a male predominance, especially in the extensive type. All patients with the extensive type were males, except for one female. The rate of tobacco smoking was higher in the extensive type, which might be explained by its male predominance. Indeed, it has been reported that smoking prevalence in South Korea is approximately 10 times higher in males than in females [26]. Tobacco smoking is the best established risk factor for bladder cancer [27], and, similarly, CG might also be associated with a smoking history. However, no study has yet demonstrated a causal relationship between smoking and CG pathogenesis.

Several cases of hydronephrosis caused by CG have been reported [10,13-19]. All these cases were males, relatively young (between 22 and 52 y), and mostly thought to have the extensive type according to the definition used in this study. All of them were managed using TUR, and in some cases, ureteral stent or percutaneous nephrostomy was required to maintain renal function [13,14,16]. Recurrent CG was managed with repeat TUR, but in severe cases, ureteral reimplantation with transureteroureterostomy or

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Table 2. Comparison of CG patients without previous history of urinary tract malignancy according to extent

Variable	Extensive (n=36)	Focal (n=74)	Test of significance[a]	p-value
Mean age (y)	40.4	57.1	-6.186[b]	0.025
Mean BMI (kg/m^2)	25.4	24.0	2.174[b]	0.863
Sex			17.962	<0.001
Male	35 (97.2)	42 (58.1)		
Female	1 (2.8)	31 (41.9)		
Smoking	21 (60.0)	26 (36.6)	5.193	0.023
Hypertension	4 (11.4)	28 (39.4)	8.726	0.003
Diabetes mellitus	1 (2.9)	8 (11.3)	2.134	0.144
Presentation				
Gross hematuria	10 (27.8)	38 (51.4)	5.472	0.019
Voiding problem	16 (44.4)	14 (18.9)	7.955	0.005
Flank pain	2 (5.6)	10 (13.5)	1.579	0.209
Microscopic hematuria	1 (2.8)	6 (8.1)	1.155	0.283
Incidentally found	11 (30.6)	15 (20.3)	1.419	0.234
Urinary stone	5 (15.6)	16 (25.8)	1.261	0.261
Hydronephrosis	6 (18.8)	10 (16.1)	0.103	0.749
Hydronephrosis by CG itself	5 (83.3)	1 (10.0)	8.604	0.003
Multiple TUR	9 (26.5)	4 (7.7)	5.650	0.017
Intestinal metaplasia	6 (16.7)	3 (4.1)	5.128	0.024
Subsequent malignancy	0 (0.0)	4 (5.4)	2.019	0.155

Values are presented as mean only or number (%).
CG, cystitis glandularis; BMI, body mass index; TUR, transurethral resection.
[a]:By chi-square test.
[b]:By independent samples t-test.

cystectomy with neobladder was performed [15-17,19]. In one case, despite CG being managed with TUR and percutaneous nephrostomy, renal function was eventually lost, and the patient had to wait for renal transplantation [14]. All six patients with hydronephrosis caused by CG in this study are summarized in Table 3. They were all males, and the location of CG was the trigone. Among them, five patients with extensive type showed bilateral hydronephrosis, which was successfully managed using TUR in four patients and with ureteroneocystostomy being performed in one patient. Regardless of whether hydronephrosis was resolved, renal function was not deteriorated in patients with the extensive type. However, in a patient with the focal type, despite two times of TUR procedures, renal function worsened, and urothelial carcinoma of the left ureter had developed at 17 months follow-up, despite initial computed tomography of this patient showing no abnormal lesions in the upper urinary tract.

The exact etiopathogenesis of CG remains unclear. However, chronic bladder inflammation, such as chronic urinary tract infections, inflammation caused by urolithiasis, outflow obstruction, and long-term indwelling catheter drainage, is thought to be the main risk factor in the development of clinically significant CG [1]. A recent study demonstrated that urinary infection, long-term indwelling catheter usage, urinary calculus, squamous metaplasia, and atypical hyperplasia were independent risk factors for CG recurrence [28]. Thus, treatment is based on the elimination of possible etiological factors that cause chronic irritation of the bladder mucosa, and the method of choice for obvious exophytic lesions is TUR [9]. Most patients with any type of CG are treated with TUR. However, because the optimal treatment of CG has not yet been established, supplementary treatments have been tried, including intravesical bacillus Calmette–Guerin, steroid instillation, or oral anti-inflammatory drug administration [18,19,29,30]. One of our patients presented with gross hematuria and left flank pain and was diagnosed with bilateral hydronephrosis caused by CG itself. He underwent TUR twice and received oral steroid administration for 10 months. Although he was successfully treated, it is unclear whether the oral steroids had a significant effect on his recovery.

This study had some limitations, including a relatively short follow-up period and a retrospective design. Although we identified some clinical differences between the two types of CG, it was impossible to optimize their manage-

Table 3. Clinical features and outcomes of the six patients with hydronephrosis caused by CG

No.	Age (y)	Sex	Past history	Presentation	Location	Extent	Laterality	HN grade	Treatments and outcomes	Renal function[a]	FU period (mo)
1	24	M	Smoker	GH Voiding difficulty	Trigone	Extensive	bil	III/III	TURB HN was not resolved, but renal function was not deteriorated.	1→1	32
2	43	M	None	GH Flank pain (Lt)	Trigone	Extensive	bil	I/I	TURB ×2 Ureteral stent insertion (5 mo) Oral steroid (10 mo) HN was resolved after treatment.	1→1	27
3	73	M	HTN	GH Flank pain (Lt)	Trigone (Lt orifice)	Focal	Lt	I	TURB ×2 HN was not resolved, and left ureter tumor was found at 17-month follow-up. Renal function was deteriorated.	2→3	30
4	33	M	None	Incidentally found	Trigone	Extensive	bil	I/I	TURB HN was not resolved, but renal function was not deteriorated.	1→1	13
5	44	M	Ex-smoker s/p UNO, bil	Flank pain (Lt)	Trigone	Extensive	bil	IV/II	PCN, bil, TURB and re-do UNO, bil Although bilateral UNO was performed under CG diagnosis at another hospital, severe HN was not resolved. Re-do UNO was performed in our institution.	3→3	81
6	36	M	None	Voiding difficulty	Trigone	Extensive	bil	I/I	TURB HN was resolved after treatment, and renal function was not deteriorated.	2→2	29

CG, cystitis glandularis; HN, hydronephrosis; FU, follow-up; GH, gross hematuria; bil, bilateral; TURB, transurethral resection of bladder; Lt, left; HTN, hypertension; s/p, status post; UNO, ureteroneocystostomy; PCN, percutaneous nephrostomy; Rt, right.

[a]:Presented as chronic kidney disease stage from initial visit to last visit.

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Table 4. Clinical features and outcomes of the patients who were subsequently diagnosed with urinary tract malignancy

No.	Age (y)	Sex	Past history	Presentation	Location	HN	Extent	Interval to diagnosis (mo)	Diagnosis
1	75	M	DM	GH Dysuria	Lateral wall (Lt)		Focal	36	Bladder, papillary urothelial carcinoma, high grade
2	58	M	Old TBc, ex-smoker	GH	Trigone (Lt orifice)		Focal	12	Bladder, papillary urothelial carcinoma, low grade
3	73	M	HTN	GH Frequency Flank pain (Lt)	Trigone (Lt orifice)	Lt	Focal	17	Lt ureter, urothelial carcinoma
4	60	M	None	GH	Trigone (Rt orifice)		Focal	6	Bladder, urothelial carcinoma, high grade Rt ureter, infiltrating urothelial carcinoma, high grade

HN, hydronephrosis; DM, diabetes mellitus; GH, gross hematuria; Lt, left; TBc, tuberculosis; HTN, hypertension; Rt, right.

Table 5. Summary of previously reported case series of CG and the present study

Reference	No.	Age (y)	M:F ratio	Presentation (%)	HN (%)	Resolution (%)	Mean FU period (y)	Outcomes
Smith et al. [3]	Total: 136 CCEG: 117 IM: 19	3 weeks–92	CCEG 2:1 IM 1.5:1	-	-	-	4.4	No evidence of increasing the future risk of malignancy. No association identified between either CCEG or IM and pelvic lipomatosis.
Agrawal et al. [4]	Total: 64 Typical: 52 IM: 12	Mean 35.6 (24–48)	Male only	Hematuria: 38 (59.4) Dysuria: 31 (48.4) Frequency: 33 (51.6) Extensive lesions beyond the trigone: 14 (21.9)	8 (12.5)	15/64 (23.4)	4.8	No differences in the symptoms or the development of malignancy between IM group or typical group of CG.
Yi et al. [5]	Total: 166 Typical: 155 Intestinal: 11	9–86	1:1 (81:85)	-	-	Intestinal group: 8/11 (72.7)	Typical group: 3.38 Intestinal group: 2.82	No subsequent malignancy in intestinal and typical CG group.
Present study	Total: 110 Focal: 74 Extensive: 36	Mean 52 (20–86) Focal: 57.1 Extensive: 40.4	2.4:1 Focal: 1.4:1 Extensive: 35:1	Gross hematuria: 48 (43.6) Voiding problem: 30 (27.3) Flank pain: 12 (10.9) Microhematuria: 7 (6.4)	16 (17.0)	50/78 (64.1) Focal: 38 (79.2) Extensive: 12 (40.0)	3.3	No subsequent adenocarcinoma, but 4 patients diagnosed with urothelial carcinoma in follow-up period. All were focal type.

CG, cystitis glandularis; M:F, male:female; HN, hydronephrosis; FU, follow-up; CCEG, cystitis cystica et glandularis; IM, intestinal metaplasia.

ment and follow-up plan according to CG type based on our experience. However, the fact that four patients with a focal type of CG were subsequently diagnosed with urothelial carcinoma cannot be disregarded. Therefore, we cautiously recommend initiating biannual cystoscopy follow-up initially, followed by annual cystoscopy thereafter, similar to other benign bladder tumor such as inverted urothelial papilloma. Future large-scale cohort studies are necessary to investigate the epidemiologic relationship between each type of CG and various factors. In addition, basic research on relevant genetic and molecular mechanisms in the development of CG is also needed.

CONCLUSIONS

There were significant differences in the clinical features between the extensive- and focal-types CG. The extensive type was more commonly associated with urologic complications, such as voiding difficulty, hydronephrosis, and multiple TUR. Male sex and smoking may be associated with the extensive type, while relatively younger age suggests that genetic factors may play a role in the pathogenesis of the extensive type of CG. Meanwhile, subsequent urinary tract malignancy was observed in several patients with focal-type CG. Thus, thorough initial work-up and careful follow-up is necessary despite the benign nature of CG. Like other benign bladder tumor such as inverted urothelial papilloma, annual surveillance cystoscopy may be appropriate.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Kang Su Cho. Data acquisition: Jee Soo Ha. Statistical analysis: Jee Soo Ha and Jinhyung Jeon. Data analysis and interpretation: Jinhyung Jeon. Drafting of the manuscript: Jinhyung Jeon. Critical revision of the manuscript: Su-Jin Shin and Kang Su Cho. Administrative, technical, or material support: Won Sik Ham and Young Deuk Choi. Supervision: Kang Su Cho. Approval of the final manuscript: all authors.

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