



Relationship between the Clinical Characteristics and Intervention Scores of Infants with Apparent Life-threatening Events

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We investigated the clinical presentations, diagnostic and therapeutic modalities, and prognosis from follow-up of infants with apparent life-threatening events (ALTE). In addition, the relationship between the clinical characteristics of patients and significant intervention scores was analyzed. We enrolled patients younger than 12 months who were diagnosed with ALTE from January 2005 to December 2012. There were 29 ALTE infants with a peak incidence of age younger than 1 month (48.3%). The most common symptoms for ALTE diagnosis were apnea (69.0%) and color change (58.6%). Eleven patients appeared normal upon arrival at hospital but 2 patients required cardiopulmonary resuscitation during the initial ALTE. The most common ALTE cause was respiratory disease, including respiratory infection and upper airway anomalies (44.8%). There were 20 cases of repeat ALTE and 2 cases of death during hospitalization. Four patients (15.4%) experienced recurrence of ALTE after discharge and 4 patients (15.4%) showed developmental abnormalities during the follow-up period. The patients with ALTE during sleep had lower significant intervention scores ($P = 0.015$) compared to patients with ALTE during wakefulness and patients with previous respiratory symptoms had higher significant intervention scores ($P = 0.013$) than those without previous respiratory symptoms. Although not statistically significant, there was a weak positive correlation between the patient's total ALTE criteria and total significant intervention score (Fig. 2, $r = 0.330$, $P = 0.080$). We recommend that all ALTE infants undergo inpatient observation and evaluations with at least 24 hr of cardiorespiratory monitoring, and should follow up at least within a month after discharge.

Keywords: Apparent Life-threatening Event; Infant; Hospitalization; Intervention

INTRODUCTION

Since the 1970s, many investigators have focused on episodes occurring in infants characterized by an acute and unexpected change in behavior either with or without apnea. These episodes were referred to as “near-misses” for sudden infant death syndrome (SIDS) (1), and considered a possible cause of SIDS. In 1986, the National Institutes of Health consensus conference named these episodes apparent life-threatening events (ALTE) and defined them using the following criteria: some combination of central or obstructive apnea; color change; marked change in muscle tone; and choking or gagging (2). It is a frightening event, occurring predominantly in infancy and accounting for 0.6%-1.7% of all emergency department (ED) visits for infants younger than 1 yr of age and 0.5%-6% of all infant visits (3-6). It is associated with a 0%-6% mortality rate (2).

In some studies, high-risk groups for ALTE were defined as 1) having events during sleep, 2) needing resuscitation, 3) having

a subsequent similar episode, 4) being siblings of SIDS patients, and 5) developing a seizure disorder. In addition, studies reported that high-risk groups for ALTE had a high mortality rate of about 25% (7). However, infants with ALTE are often asymptomatic on arrival at the hospital and the natural course of ALTE has recently been reported to be more benign (8). To date, it has been difficult to find reports of ALTE infants in Korea.

In this study, we investigated the clinical presentations, diagnostic and therapeutic modalities, and prognosis from follow-up of infants with ALTE. In addition, the relationship between the clinical characteristics of patients and significant intervention scores was analyzed.

MATERIALS AND METHODS

Patients

We enrolled patients younger than 12 months who were diagnosed with ALTE from January 2005 to December 2012. ALTE

was diagnosed if the patient had least 1 of the following: apnea, color change, change in muscle tone, or choking or gagging. All patients were admitted for evaluation and medical intervention, and patients' medical records were retrospectively reviewed. The patients' characteristics, status upon hospital arrival, description of the event, diagnostic investigation, medical treatment, clinical outcome, and final diagnosis were investigated.

Laboratory tests

In order to identify the underlying cause of ALTE, various diagnostic investigations were performed during hospitalization. On the day of admission, blood samples were analyzed for complete blood count (CBC) with bacterial culture, blood gas analysis with electrolytes, and C-reactive proteins. In addition, respiratory virus reverse transcription polymerase chain reaction (RV RT-PCR) using nasopharyngeal aspirate, Rotavirus antigen test in stool, urinalysis with culture, cerebrospinal fluid (CSF) analysis, and chest radiography were all utilized. RV RT-PCR included tests for metapneumovirus, adenovirus (A-F), coronavirus 229E/OC43, parainfluenza virus 1/2/3, influenza A/B virus, rhinovirus, respiratory syncytial virus A/B, and bocavirus. Electrocardiograms (ECG), 2-dimensional echocardiograms, upper gastrointestinal studies, electroencephalograms (EEG), brain image studies, and tests for metabolic disease were ordered on an individual patient basis.

Scoring for significant intervention

A confirmed bacterial or viral infection, abnormal chest radiographic finding, ECG, 2-dimensional echocardiogram, upper gastrointestinal study, EEG, brain image study, and any test to characterize metabolic disease were classified as significant diagnostic interventions. Supplemental oxygen, stimulation, endotracheal intubation, parenteral antibiotics, and cardiopulmonary resuscitation (CPR) were classified as significant medical interventions. Recurrence of ALTE and death during hospitalization were also classified as significant interventions. Each intervention was rated 1 point, and we totaled the significant interventions on a scale from 0-16.

Table 1. Demographic characteristics of the patients

Variables	Values
Sex (M:F) (number)	16:13
Age (days) (median, range)	39.0 (3-220)
Weight (gram) (median, range)	3,730 (2,430-7,820)
Preterm (number)	12 (41.4%)
Low birth weight (number)	8 (27.6%)
Maternal age (yr) (median, range)	31.0 (25-42)
Maternal smoking (number)	0 (0%)
Feeding (breast milk:formula:mixed) (number)	9:9:11
Birth order (1st:2nd:3rd) (number)	15:12:2

M, male; F, female; OPD, out-patient department; ED, emergency department.

Statistical analysis

All statistical analyses were performed using SPSS version 21.0 (SPSS for Windows, version 21.0, SPSS Inc., Chicago, IL, USA), and all values were described as frequencies and median with range. The Mann-Whitney U-test was applied to compare significant intervention scores according to patients' clinical characteristics. Spearman rank correlation coefficient (r) was applied to analyze correlation between patients' characteristics and significant intervention scores. A value of $P < 0.05$ was considered statistically significant.

Ethics statement

This study was approved by the institutional review board of the Keimyung University Dongsan Medical Center (IRB No. 2014-09-054). Informed consent was exempted by the board.

RESULTS

Demographic characteristics of the patients

There were 29 patients (16 boys and 13 girls) who met the criteria for ALTE (Table 1). The median patient age was 39.0 days (range, 3-220 days), with a peak incidence of age younger than 1 month (48.3%) and 69.0% of patients younger than 2 months (Fig. 1). Twelve patients (41.4%) were preterm infants, and 8 (27.6%) were low birth weight infants. Among 12 preterm infants, the median gestational age was 35.5 weeks (range, 27.5-36.3 weeks), and 2 patients were diagnosed as bronchopulmonary dysplasia and 2 patients were diagnosed as apnea of prematurity. Fifteen infants (51.7%) were firstborn. The median maternal age was 31.0 yr (range, 25-42 yr) and no mother presented with a history of smoking. There was no history of SIDS

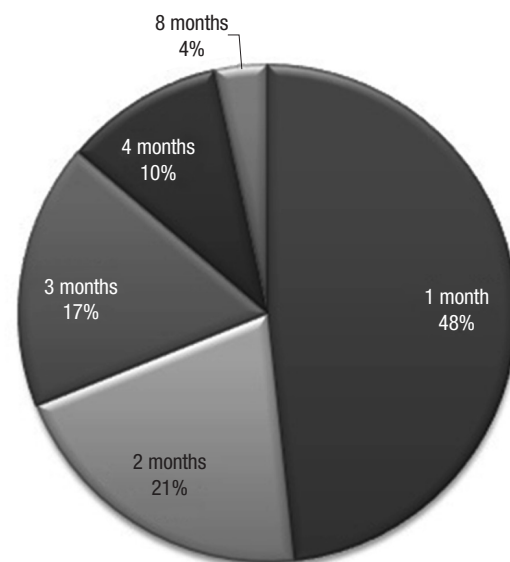


Fig. 1. Age of patients. Peak incidence of age was younger than 1 month (48.3%); 69.0% of patients were younger than 2 months.

Table 2. Clinical presentation of ALTE event

Clinical findings	No. (%) of patients
Pre-event condition	
Fever	3 (10.3)
URI symptom	17 (58.6)
Event criteria	
Apnea	20 (69.0)
Color change	17 (58.6)
Change in muscle tone	9 (31.0)
Choking	6 (20.7)
Gagging	3 (10.3)
Route on hospital (OPD:ED)	12 (41):17 (59)
Time of arrival (day:night)	20 (69):9 (31)

URI, upper respiratory infection.

or ALTE in their siblings.

Clinical characteristics of the patients' event

There was a recent history of fever in 2 patients, respiratory symptoms in 16, and both in 1. Ten patients did not have any specific history. Twenty-seven patients had an event at home. After the event, 12 patients visited an ED, and 17 patients visited an outpatient department (OPD). Twenty patients arrived at the hospital during the day, while 9 arrived at night. Eleven patients appeared normal upon their clinical examination at the time of arrival, whereas 2 patients required CPR during the initial ALTE and 4 were transferred from other hospitals while intubated. Other 12 patients showed sick appearance such as cyanosis, grunting, chest retraction and atonic posture.

The predominant symptoms for ALTE diagnosis were apnea and color change in 20 (69.0%) and 19 (58.6%) patients, respectively (Table 2). Change in muscle tone occurred in 9 (31.0%), choking in 6 (20.7%), and gagging in 3 (10.3%). The events occurred while sleeping in 5 and while awake in 24. Of the 24 patients, the events occurred during and after feeding in 4, and with crying in 3. In the other 17 patients, the specific situation associated with the event was not found in medical records.

Interventions in hospital

Eight patients had confirmed bacterial infections such as *Enterobacter* or *Escherichia coli* in urine in 3 patients, *Staphylococcus* or *Streptococcus* in blood in 3 patients, and *Streptococcus* in both blood and CSF in 2 patients. Although not statistically significant, the patients with confirmed bacterial infection showed higher incidence of fever than the other patients (25.0% vs. 4.8%, $P = 0.176$). Also, in laboratory test, they showed higher level of white blood cell (WBC) count ($11,156.3 \pm 5,066.3/\mu\text{L}$ vs. $9,699.0 \pm 3,543.7/\mu\text{L}$, $P = 0.388$) and C-reactive protein (CRP) (3.4 ± 5.1 mg/dL vs. 0.4 ± 0.5 mg/dL, $P = 0.135$) than the other patients. RV RT-PCR was performed for 11 patients, and several viruses were identified in 8 patients: respiratory syncytial virus in 3, human rhinovirus in 3, human parainfluenza virus in 3, and bocavirus in 1. Rotavirus antigen test showed positive result in 1 patient.

Table 3. Therapeutic and diagnostic intervention of the patients

Interventions	No. of patients
Diagnostic intervention	
Confirmed bacterial infection	8
Confirmed viral infection	9
Chest x-ray (normal:abnormal)	29 (18:11)
ECG (normal:abnormal)	10 (10:0)
UGI study (normal:abnormal)	8 (1:7)
EEG (normal:abnormal)	14 (10:4)
2D-Echocardiography (normal:abnormal)	9 (7:2)
Brain image study (normal:abnormal)	14 (8:6)
Test for metabolic disease (normal:abnormal)	5 (5:0)
Therapeutic Intervention	
Oxygen supply	18
Stimulation	18
Tracheal intubation	11
Antibiotics	17
CPR	2

ECG, electrocardiogram; UGI, upper gastrointestinal; EEG, electroencephalogram; CPR, cardiopulmonary resuscitation.

Primary medical management for ALTE was supplemental oxygen and stimulation, each given to 18 patients (Table 3). Eleven patients needed mechanical ventilator support with endotracheal intubation because of recurrent apnea in 9 patients, dyspnea in 1, and a CPR situation in 1. The median duration of ventilator care was 2.0 days (range, 1-25 days). Seventeen patients were treated with parenteral antibiotics for a suspected bacterial infection, including culture-confirmed bacterial infection. Infections were suspected to be pneumonia with respiratory symptoms in 11, sepsis with fever or shock in 4, and urinary tract infections with pyuria in 2. Two patients required CPR because of bradycardia and hypotension during the initial ALTE, but recovered.

After analyzing the relationship between the patients' clinical characteristics and significant intervention scores, we saw that patients with ALTE during sleep had significantly lower scores (Fig. 2, $P = 0.015$) compared to patients with ALTE during wakefulness. We also saw that patients with previous respiratory symptoms had significantly higher scores (Fig. 2, $P = 0.013$) than those without previous respiratory symptoms. Although not statistically significant, there was a weak positive correlation between the patient's total ALTE criteria and total significant intervention score (Fig. 3, $r = 0.330$, $P = 0.080$).

The causes of ALTE and inpatient outcome

Table 4 summarizes the common causes of ALTE. The most common ALTE cause was respiratory disease, including respiratory infection in 10 patients and upper airway anomalies in 3. The next most common cause was neurologic disease such as a convulsive disorder, congenital hypoventilation syndrome, and Haddad syndrome. Three patients had confirmed bacterial meningitis and sepsis. Gastroesophageal reflux (GER)-related ALTE was diagnosed in 3 patients, prematurity-related causes in 2, previously known congenital heart disease-related ALTE in 1,

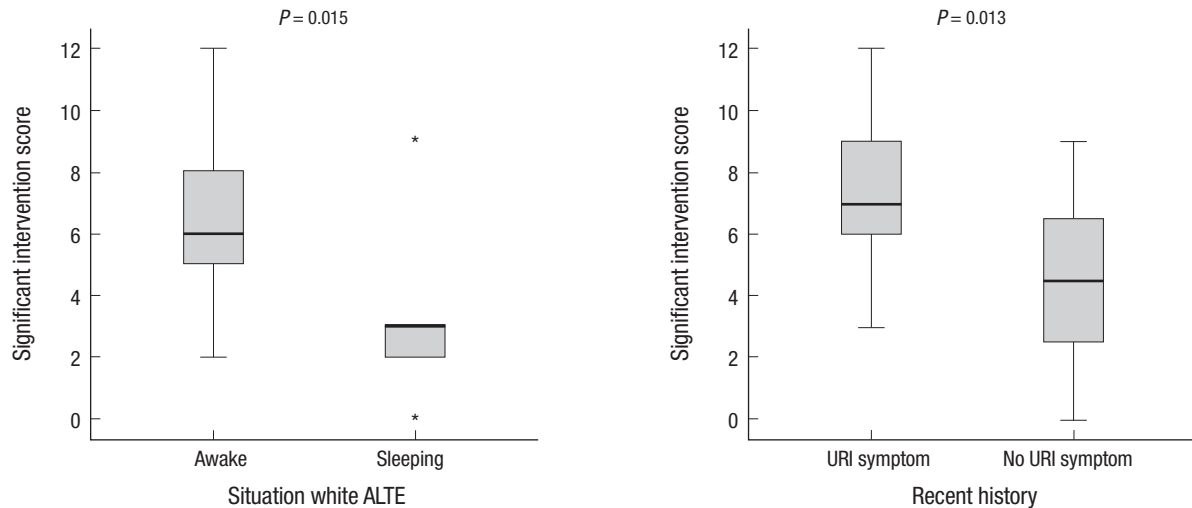


Fig. 2. Significant intervention scores according to ALTE situation and recent URI history. The patients with ALTE during sleep had significantly lower scores ($P = 0.015$) compared to patients with ALTE during wakefulness, and the patients with previous respiratory symptoms had significantly higher scores ($P = 0.013$) than those without previous respiratory symptoms.

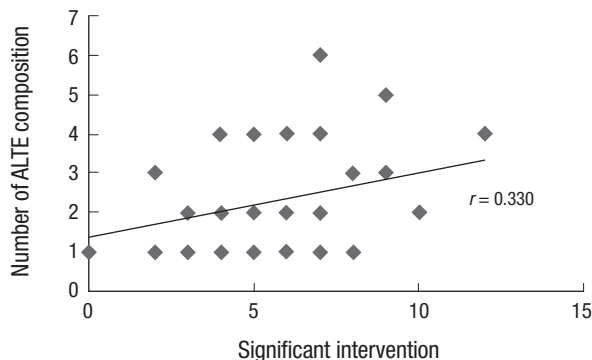


Fig. 3. Relationship between total significant intervention scores and number of ALTE criteria. There was a positive correlation between increasing ALTE criteria and total significant intervention score ($r = 0.330$, $P = 0.080$).

and sedative medication-related ALTE in 1. Two cases of ALTE remained unexplained.

The median duration of hospitalization was 8.0 days (range, 2-38 days), and 20 patients (69.0%) showed repeat ALTE in the hospital. There were 2 cases of death, resulting in an overall mortality rate of 6.9%. One death caused by group B streptococcal meningitis occurred at 25 days after admission. Both CSF and blood culture confirmed his streptococcal infection, and abnormal findings were also seen in his EEG and brain sonography. The other death with unexplained ALTE occurred at 18 days after admission. She had preterm birth and low birth weight history and diagnosed as bronchopulmonary dysplasia previously.

Prognosis from follow up

Except for 3 patients, 26 patients had a follow-up at an OPD and the median duration of follow-up was 6.0 months (range, 1-52 months). There were no cases of mortality after discharge, although 4 cases (15.4%) experienced recurrence of ALTE after

Table 4. The causes of the ALTE

Causes	No. of patients
Respiratory	
Infection	10
Vocal cord palsy	1
Laryngomalacia	1
Narrowing of supraglottic larynx	1
Neurologic	
Convulsive disorder	2
Congenital hypoventilation syndrome	1
Haddad syndrome	1
Infection	
GBS meningitis	2
Sepsis	1
Gastrointestinal	
Gastroesophageal reflux	3
Prematurity related	
Apnea of prematurity	2
Cardiovascular	
Congenital heart disease	1
Medication	
Sedative agent	1
Unknown	2

GBS, Group B *Streptococcus*.

discharge, all of whom also showed recurrent ALTE in the hospital. The characteristics of recurrent ALTE are described in Table 5. Four patients (15.4%) showed developmental abnormalities during the follow-up period. Their final diagnoses were pneumonia with prematurity history in 2, Haddad syndrome in 1, and narrowing of supraglottic larynx with GER grade III in 1.

DISCUSSION

In the present study, we identified the heterogeneity of ALTEs; some patients often appeared healthy upon arrival in the ED or OPD, while some patients required immediate CPR. This het-

Table 5. The patients with recurrent ALTE after discharge

Final diagnosis	FU duration (months)	Duration of recurrent ALTE	Management at home	Development
1 Pneumonia, BPD	8	-11 days	Home O ₂	Normal
2 Congenital hypoventilation syndrome	16	-4 days	Aminophylline	Normal
3 Haddad syndrome	1	-4 days	Home O ₂ with ventilator	Delay
4 Narrowing of supraglottic larynx, GER grade III	24	-22 months	Tube feeding	Delay

FU, follow up; ALTE, apparent life-threatening event; BPD, bronchopulmonary dysplasia; GER, Gastroesophageal reflux; O₂, oxygen.

erogeneity causes difficulties for clinicians deciding how to manage patients with ALTE. The admission rate for ALTE is usually 75%-100% (9-12), reflecting the recommendations of many centers that all patients with ALTE be admitted for a period of inpatient observation. Some studies suggested that the major indicators of admission and further evaluation were prematurity, age younger than 30 days or older than 60 days, history of other illness, recurrent ALTE, and abnormal result in the initial examination (4, 9, 10). In our study, the admission rate of ALTE infant was 100% and duration of hospital stay was 2-38 days.

In previous studies, the causes of ALTE were grouped into gastrointestinal (50%), neurological (30%), respiratory (20%), cardiovascular (5%), metabolic and endocrine (2%-5%), and others such as child abuse (13, 14). The most common diagnosis was gastrointestinal disease, including GER. Al Khushi et al. (15) reported that the most important diagnoses of ALTE included serious bacterial infections, seizures, child abuse, metabolic disorders, and severe apnea with hypoxemia. Among the infectious causes of ALTE, reported prevalences were about 0%-1.6% for meningitis, 0%-2.5% for bacteremia, 0%-7.6% for urinary tract infection, 0%-10% for lower respiratory tract infection, and 9%-82% for bronchiolitis (5, 16-19). About 35%-50% of ALTE cases had no diagnosable cause, despite a medical history and complete evaluation (12, 13). In contrast to previous studies, the present study showed that the most common discharge diagnosis was respiratory disease, including respiratory infection, followed by neurological disease. Two patients' ALTEs (6.9%) remained unexplained.

In a review of several studies, Tieder et al. (20) demonstrated that the most frequently evaluated diagnostic tests were for GER, neurologic abnormalities, anemia, infections, toxic ingestions, metabolic disorders, and cardiac dysrhythmias. There was no evidence to recommend routine nonspecific tests such as CBC, serum glucose, or electrolyte levels (20). On the other hand, Vandenplas et al. (21) suggested that, although GER was considered a major cause of ALTE, routine GER testing is unnecessary in children with ALTE. The incidence of GER is generally high in infancy regardless, and a positive result is not a confirmation of a relationship between GER and ALTE. In our study, 8 patients

underwent an upper gastrointestinal study because 4 had been previously diagnosed with GER, 2 had feeding-related ALTE, 1 had a history of esophageal atresia with tracheoesophageal fistula, and 1 had recurrent pneumonia. Seven patients showed positive signs of GER (grade I in 2, grade II in 3, grade III in 2), but GER was only confirmed as a cause of ALTE at discharge in 3 patients. In this regard, our results were similar to the previous study.

Many studies have investigated potential predictors of subsequent events in ALTE patients. Some studies identified a history of prematurity and multiple ALTEs as risk factors for a serious underlying condition or poor prognosis (10, 11). Davies et al. (4) found that more serious diagnosis was associated with a presentation age greater than 2 months, abnormal initial clinical examination, and recurrent ALTE. Mittal et al. (12) reported that 12% of ALTE infants needed significant intervention during hospitalization, and that prematurity, abnormal results from the physical examination, color change to cyanosis, absence of symptoms of upper respiratory tract infection, and absence of choking were all predictors of significant intervention. In order to determine whether to discharge patients from the ED, the authors recommended a clinical decision rule based on components of patient history and examination findings that have been established as significant predictors.

In this study, we analyzed the relationship between the patients' clinical characteristics and total significant intervention scores. We identified the following results: 1) ALTE occurring during sleep had a low incidence of significant interventions, 2) ALTE with a recent history of respiratory symptoms had a high incidence of significant intervention, and 3) patients with numerous signs of ALTE criteria had high scores of significant intervention ($r = 0.330$). Risk factors, such as prematurity, which had been described as poor prognosis factors in previous studies, did not show statistical significance in relation to the significant intervention scores. This result was somewhat different from previous studies, and we thought that it was caused by the difference of underlying diagnosis of ALTE. In our study, the most common ALTE cause was respiratory disease (44.8%), and these patients may show the more symptoms while awake.

In previous studies of ALTE prognosis after discharge, the mortality rate was 0%-0.5% during 12-60 months of follow-up (3, 9, 22, 23). Recently, Kant et al. (24) reported a mortality after discharge of 1.1% (2 deaths/174 infants) during 34 months of follow-up, with 2 deaths occurring within 15 days of discharge. Bonkowsky et al. (22) studied the recurrence of ALTE and found that 71% of the initial patients with ALTE returned to the hospital within 1 month with a second event. This study showed the importance of close follow-up after discharge. The authors also found that 5% of patients developed adverse neurological outcomes, including chronic epilepsy and developmental delays. Nunes et al. (25) reported that among 56 patients with ALTE,

51.5% showed normal outcome, 4 showed repeated ALTE, and none reported deaths due to SIDS. The authors concluded that the outcome is generally related to the associated underlying disease. We found no cases of mortality after discharge, but there were 4 cases (15.4%) of recurrent ALTE after discharge occurring nearly within 2 weeks. During the median 6-month follow-up period, 4 patients (15.4%) showed developmental abnormalities, although we could not definitively identify the relationship between developmental delay and ALTE relapse.

Our study had several limitations. The present study was a small sized retrospective study, and patients' data were collected only from a retrospective chart review. Accordingly, we could have missed some portion of ALTE patients. The number of deaths was too small to analyze any potentially significant difference of clinical course according to death.

Considering that ALTE encompasses a wide range of clinical presentations, we recommend that all ALTE infants undergo inpatient clinical observation and evaluations with at least 24 hr of cardiorespiratory monitoring. In addition, ALTE infants should be followed up at least within a month after discharge. Long-term follow-up should be decided on an individual basis according to the underlying status of the patients.

DISCLOSURE

The authors have no conflicts of interest in this work.

AUTHOR CONTRIBUTION

Conception and coordination of the study: Kim YH. Design of the study and ethical issues: Kim YH, Choi HJ. Acquisition of data: Kim YH, Choi HJ. Statistical analysis: Choi HJ. Manuscript preparation: Choi HJ. Manuscript approval: Kim YH.

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