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ORIGINAL ARTICLE

Efficacy of Vitamin and Antioxidant Supplements in Prevention of Esophageal Cancer: Meta-analysis of Randomized Controlled Trials

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Background: Observational epidemiological studies have shown that higher intakes of vitamins or antioxidants were inversely associated with the risk of esophageal cancer. However, randomized controlled trials (RCTs) have reported no preventive efficacy of vitamin or antioxidant supplements on esophageal cancer. This meta-analysis aimed to investigate the efficacy of vitamin and antioxidant supplements in the prevention of esophageal cancer as reported by RCTs.
Methods: We searched PubMed, EMBASE, and the Cochrane Library in May 2013. Two authors independently reviewed and selected eligible articles based on predetermined selection criteria.
Results: Of 171 articles searched from three databases and relevant bibliographies, 10 RCTs were included in the final analyses. In a fixed-effect meta-analysis of 10 trials, there was no efficacy of vitamin and antioxidant supplements in the prevention of esophageal cancer (relative risk [RR], 1.04; 95% confidence interval [CI], 0.86-1.25; I^2=0.0%). Also, subgroup meta-analyses showed that vitamin and antioxidant supplements had no preventive efficacy on esophageal cancer both in the high risk (RR, 1.04; 95% CI, 0.85-1.28; n=4) and non-high risk (RR, 1.01; 95% CI, 0.65-1.56; n=6) groups for esophageal cancer. Further, subgroup meta-analyses revealed no preventive efficacy on esophageal cancer by type of methodological quality and type of vitamin and antioxidant supplements.
Conclusions: Unlike observational epidemiological studies, this meta-analysis of RCTs suggests that there is no clinical evidence to support the efficacy of vitamin and antioxidant supplements in the prevention of esophageal cancer. **(J Cancer Prev 2013;18:135-143)**

Key Words: Vitamin supplements, Antioxidant supplements, Esophageal cancer, Randomized controlled trials, Meta-analysis

INTRODUCTION

According to GLOBOCAN 2008 published by the International Agency for Research on Cancer, esophageal cancer is the eighth most common cancer, with 3.8% of all cancer cases, and the sixth leading cause of death from cancer, with 5.4% of all cancer deaths worldwide estimated in 2008.[1] Along with genetic causes, lifestyle and environmental factors are considered to be important in the development of esophageal cancer.[2] Among lifestyle factors, fruits and vegetables are rich in vitamins or antioxidants, which may have anticarcinogenic activities by various mechanisms removing free radicals and inhibiting the formation of N-nitroso compounds.[2-4]

Previous epidemiological studies have investigated the association between the risk of esophageal cancer and the intake of fruits and vegetables rich in vitamins and antioxidants, and those findings are mixed. In 2006, a

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meta-analysis of 10 epidemiological studies (1 cohort and 9 case-control studies) suggested that higher consumption of vitamin C and beta-carotene was significantly associated with a decreased risk of esophageal adenocarcinoma with odds ratios of 0.49 and 0.46, respectively.[5]

In the meantime, several randomized controlled trials (RCTs)[6-15] have reported the association between vitamin or antioxidant supplements and the risk of esophageal cancer. However, no RCTs have suggested that there was any preventive efficacy of vitamin or antioxidant supplements on esophageal cancer. Further, there has been no quantitative meta-analysis of RCTs on this issue reported so far.

The purpose of this study was to examine the quantitative preventive efficacy of vitamin and antioxidant supplements on esophageal cancer by using a meta-analysis of RCTs by type of vitamin or antioxidant supplements, methodological quality, and high risk or non-high risk groups for esophageal cancer.

MATERIALS AND METHODS

1. Data search

We searched PubMed, EMBASE, and the Cochrane Library in May 2013, by using keywords related to vitamin and antioxidant supplements and esophageal cancer in RCTs. Also, the bibliographies of relevant articles were searched in order to locate additional studies. We used the following keywords for the literature search: "vitamin," "antioxidant," "beta-carotene," or "selenium; and "esophageal cancer."

2. Selection criteria

We included RCTs that reported the preventive efficacy of vitamin or antioxidant supplements on esophageal cancer. The main outcome measure was cancer incidence.

3. Selection of relevant trials

Two evaluators (Dr. Myung SK, Dr. Yang HJ) independently screened all the studies searched from the three databases. We tried to contact the authors of the articles with insufficient data. From the trials included in the final analysis, we extracted the following data: study name, journal, country, duration of supplement treatment and follow-up period (years), population (project name), supplement interventions, relative risk (RR) with 95% confidence intervals (CI), and number of cancer/number of participants in each intervention group.

4. Main and subgroup analyses

We examined the efficacy of vitamin and antioxidant supplements administered singly or in combination with other vitamin or antioxidant supplements on esophageal cancer, compared with placebo administration in all 10 trials. Also, we evaluated those efficacy by type of vitamin or antioxidant supplements, methodological quality, and high risk or non-high risk groups for esophageal cancer.

5. Assessment of methodological quality

We also evaluated the methodological quality of the trials by using the Jadad scale.[16] This 5-point scale consists of randomization (2 points), double-blind (2 points), and follow-up (dropouts and withdrawals; 1 point) in the report of a RCT. A trial with the score of 2 or less was considered as having low-quality, and the one with the score of 3 to 5 was considered as having high-quality.

6. Statistical analyses

The pooled RR with 95% CI was calculated on the basis of both the fixed- and random-effects models; the Mantel-Haenszel method was used in the fixed-effects model, and the DerSimonian and Laird method was used in the random-effects model. We estimated heterogeneity (between-studies variability) using the Higgins I^2 statistic, which measures the percentage of total variation across studies due to heterogeneity rather than chance.[17,18] I^2 was calculated as follows:

$$I^2=100\% \times (Q-df)/Q,$$

where Q is Cochran's heterogeneity statistic and df is the degrees of freedom corresponding to it. Cochran's Q statistic was calculated as follows:

$$Q=\sum (\theta i-\theta p)^2 w_i,$$

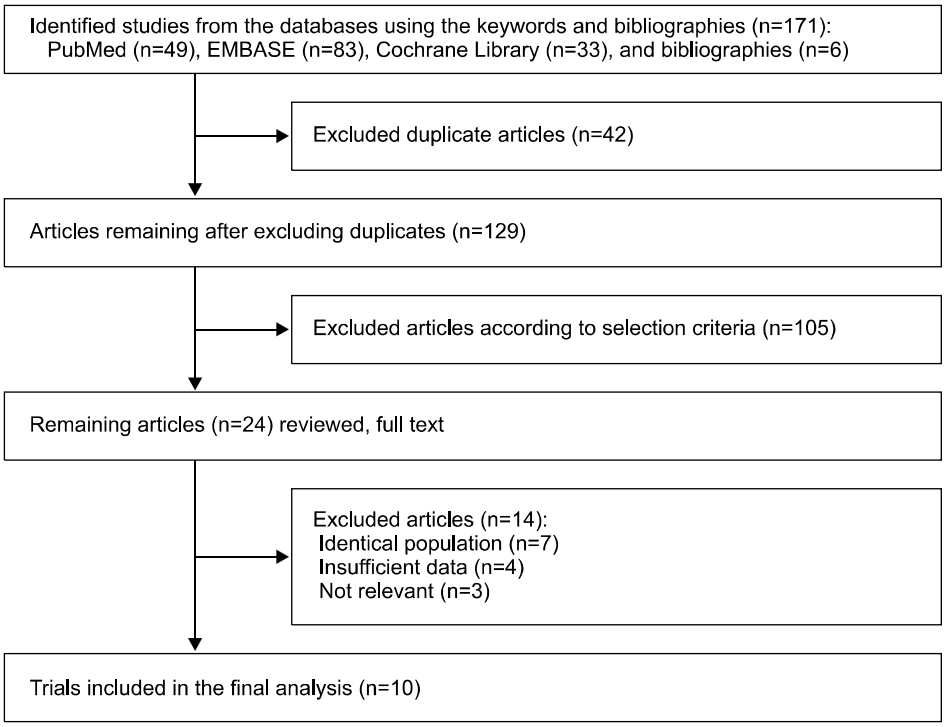

Fig. 1. Flow diagram for identification of relevant studies.

where θ i is the RR of each ith trial, θ p is the pooled RR of all the trials, and wi is the inverse variance of each ith trial as a weight. Negative values of I^2 are set at zero so that I^2 ranges between 0% (no observed heterogeneity) and 100% (maximal heterogeneity). We considered an I^2 value greater than 50% as indicating substantial heterogeneity. When there was no substantial heterogeneity, we reported the pooled estimate calculated based on the fixed-effects model. When there was substantial heterogeneity, we reported the pooled estimate calculated based on the random-effects model.

We estimated publication bias by using Begg's funnel plot and Egger's test. When the P-value was less than 0.05 by Egger's test, the presence of a publication bias was considered. We used the Stata SE version 10.0 software package (StataCorp, College Station, Texas, USA) for statistical analysis.

RESULTS

1. Selection of trials

A total of 171 articles were retrieved after searching three databases and relevant bibliographies (Fig. 1). After excluding duplicated articles and reviewing articles based on those title and abstracts, we reviewed 24 articles with those full texts and then included 10 trials in the final analysis. We excluded 14 articles because of identical populations (n=7), insufficient data (n=4), and studies not relevant to our subject (n=3).

2. General characteristics of trials

A total of 126,828 subjects with the 70,959 vitamin and antioxidant supplement and 55,869 placebo groups from 10 RCTs. As shown in Table 1, the selected trials were published from 1985 through 2007, spanning 22 years. The countries in which the studies were performed were as follows: US (n=3), China (n=3), Finland (n=1), Canada (n=1), UK (n=1), and France (n=1). The periods of treatment and follow-up ranges between 2 and 10.1 years. All trials used placebos as a control group. The types of vitamin and antioxidant supplements were vitamin A, vitamin B2, Vitamin C, vitamin E, beta-carotene, and selenium.

3. Efficacy of vitamin or antioxidant supplements in all 10 trials

In a fixed-effects model meta-analysis of all 22 trials, there was no efficacy of vitamin and antioxidant supplements in the prevention of esophageal cancer (RR, 1.04;

Table 1. General characteristics of trials included in the final analysis (n=10)

	Study name (no. of reference)	Journal	Country	Duration of supplement treatment/ follow-up period (years)	Population	Supplement Interventions	RR (95% CI)	No. of esophageal cancer/no. of participants in each group
1	1985 Munoz et al.[6]	Lancet	China	1.1/1.1	610 subjects who live in the high risk of area	15 mg of retinol (vitamin A), 200 mg of riboflavin (vitamin B2), and 50 mg of zinc vs. placebo per day	Not stated	Vitamin supplements: 4/305 Placebos: 3/305
2	1993 NIT[7]	J Natl Cancer Inst	China	6/6	3,318 persons with of esophageal dysplasia	15 mg of beta-carotene and a combination of 10,000 IU of vitamin A, 180 mg of vitamin C, 60 IU of vitamin E, 50 μg of selenium, etc. vs. placebo per day	0.96 (0.76-1.22)	Vitamin and antioxidant supplements: 123/1657 Placebos: 1281/1661
3	1996 NPC[8]	JAMA	U.S.	4.5/6.4	1,312 patients with a history of basal cell or squamous cell carcinomas of the skin	200 μg of selenium vs. placebo per day	0.34 (0.07-1.66)	Selenium supplements: 2/653 Placebos: 6/659
4	2002 HPS[9]	Lancet	U.K.	5/5	20,536 adults with coronary disease, other occlusive arterial disease, or diabetes	A combination of 600 mg of vitamin E, 250 mg vitamin C, and 20 mg beta-carotene vs. placebo per day	1.19 (0.71-2.01)	Antioxidant supplements: 31/10269 Placebos: 26/10,267
5	2003 Zhu et al.[10]	Chin Med J	China	2/6	216 patients with atrophic gastritis	20 mg of folate, 30 mg of natural beta-carotene, or 30 mg of synthetic beta-carotene vs. placebo per day	0.15 (0.01-3.72)	Folate or beta-carotene supplements: 0/118 Placebos: 1/54
6	2004 CARET[11]	J Natl Cancer Inst	U.S.	4/4	18,314 participants at high risk for lung cancer because of a history of smoking or asbestos exposure	A combination of 30 mg of beta-carotene and 25,000 IU retinyl palmitate (vitamin A) vs. placebo per day	1.43 (0.90-2.29)	Beta-carotene and vitamin A supplements: 44/9,420 Placebos: 29/8,894

Table 1. Continued

	Study name (no. of reference)	Journal	Country	Duration of supplement treatment/ follow-up period (years)	Population	Supplement Interventions	RR (95% CI)	No. of esophageal cancer/no. of participants in each group
7	2004 SUVIMAX[12]	Arch Intern Med	France	7.5/7.5	13,017 French adults	A combination of 120 mg of vitamin C, 30 mg of vitamin E, 6 mg of beta-carotene, 100 μg of selenium, and 20 mg of zinc vs. placebo per day	1.01 (0.14-7.16)	Antioxidants supplements: 2/6,481 Placebos: 2/6,536
8	2005 Bairati et al.[13]	J Natl Cancer Inst	Canada	4.3/4.3	540 patients with stage or head and neck cancer treated by radiation therapy	400 IU of vitamin E and 30 mg of beta-carotene vs. placebo per day	0.98 (0.06-15.56)	Antioxidants supplements: 1/273 Placebos: 1/267
9	2005 WHS[14]	JAMA	U.S.	10.1/10.1	39,876 apparently healthy US women	600 IU of natural-source vitamin E or aspirin vs. placebo on alternate days	1.33 (0.30-5.96)	Vitamin E supplements: 47/19,937 Placebos: 3/19,939
10	2007 ATBC[15]	Cancer	Finland	6.1/6.1	29,133 male smokers	50 mg of alpha-tocopherol or 20 mg of beta-carotene vs. placebo per day	0.81 (0.34-1.95)	Antioxidant supplements: 17/21,846 Placebo: 7/7,287

RR, relative risk; CI, confidence interval; NIT, the nutrition intervention trial; NPC, the nutritional prevention of cancer study; HPS, the heart protection study; CARET, the beta-carotene and retinol efficacy trial; SUVIMAX, the supplemenatation en vitamines et mineraux antioxydants; WHS, the women's health study; ATBC, the alpha-tocopherol beta-carotene cancer prevention study.

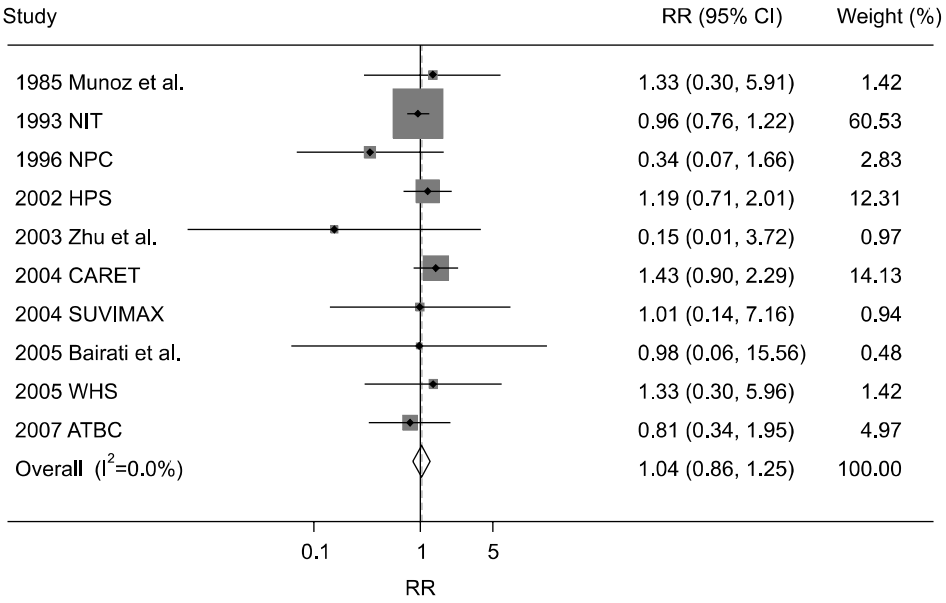

Fig. 2. Efficacy of vitamin and antioxidant supplements in prevention of esophageal cancer by a fixed-effect model meta-analysis of randomized controlled trials. RR, relative risk; CI, confidence interval; NIT, the nutrition intervention trial; NPC, the nutritional prevention of cancer study; HPS, the heart protection study; CARET, the beta-carotene and retinol efficacy trial; SUVIMAX, the supplemenatation en vitamines et mineraux antioxydants; WHS, the women's health study; ATBC, the alpha-tocopherol beta-carotene cancer prevention study.

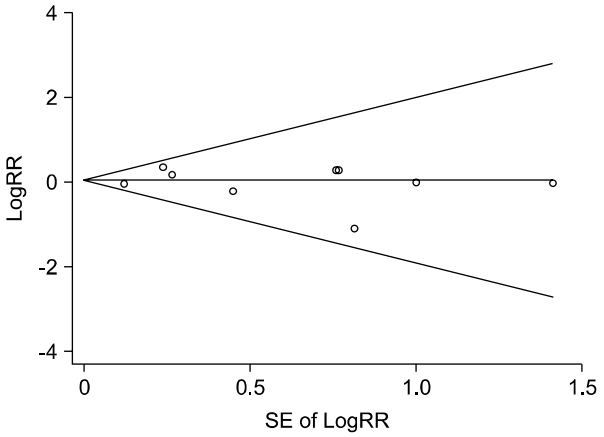

Fig. 3. Funnel plots and egger's test for identifying publication bias (P=.913) in a meta-analysis of trials (n=9). RR, relative risk; SE, standard error.

95% CI, 0.86-1.25; I^2=0.0%) (Fig. 2). There was no evidence of publication bias in the selected studies (Egger's test, P for bias=0.913; The Begg's funnel plot was symmetrical) (Fig. 3).

4. Methodological quality of trials

Table 2 shows the methodological quality of trials based on the Jadad scale. Eight trials received 4 or higher points and were classified as having a high quality, whereas two trials received 3 points and were classified as having a low quality.

5. Subgroup meta-analyses by type of supplements

In the subgroup meta-analyses by type of supplements based on the fixed-effect model, none of the antioxidant supplements had any significant preventive efficacy in the prevention of esophageal cancer: vitamin A (RR, 1.06; 95% CI, 0.86-1.30; n=3), vitamin B2 (RR, 1.33; 95% CI, 0.30-5.91; n=1), vitamin C (RR, 1.00; RR, 0.81-1.24: n=3), vitamin E (RR, 1.00; 95% CI, 0.81-1.22; n=6), folate (RR, 0.41; 95% CI, 0.02-9.76), beta-carotene (RR, 1.05; 95% CI, 0.87-1.27; n=7), and selenium (RR, 0.94; 95% CI, 0.74-1.18; n=3) (Table 3).

6. Subgroup meta-analyses by type of quality and risk group

The subgroup meta-analyses by type of quality showed no preventive efficacy of vitamin and antioxidant supplements on esophageal cancer for both high quality (RR, 1.06; 95% CI, 0.87-1.28; n=8) and low quality (RR, 0.70; 95% CI, 0.31-1.61; n=2) trials. Similarly, no preventive efficacy was found in both high risk (RR, 1.04; 95% CI, 0.85-1.28; n=4) and non-high risk (RR, 1.01; 95% CI, 0.65-1.568; n=6) groups for esophageal cancer.

DISCUSSION

The current meta-analysis of RCTs found that there was

Table 2. Methodological quality of trials based on the jadad scale (n=10)

	Source (project name)	Randomization	Description of randomization methods	Double-blind	Using identical placebo	Follow-up reporting	Total score
1	1985 Munoz et al.	1	0	1	1	1	4
2	1993 NIT	1	0	1	1	1	4
3	1996 NPC	1	0	1	1	1	4
4	2002 HPS	1	1	1	1	1	5
5	2003 Zhu et al.	1	0	1	1	0	3
6	2004 CARET	1	0	1	1	1	4
7	2004 SUVIMAX	1	0	1	1	1	4
8	2005 Bairati et al.	1	1	1	1	1	5
9	2005 WHS	1	0	1	1	1	4
10	2007 ATBC	1	0	1	1	0	3

NIT, the nutrition intervention trial; NPC, the nutritional prevention of cancer study; HPS, the heart protection study; CARET, the beta-carotene and retinol efficacy trial; SUVIMAX, the supplemenatation en vitamines et mineraux antioxydants; WHS, the women's health study; ATBC, the alpha-tocopherol beta-carotene cancer prevention study.

Table 3. Efficacy of vitamin and antioxidant supplements in prevention of esophageal cancer in subgroup meta-analyses

Variable	No. of trials	Summary RR (95% CI)	Heterogeneity, I^2	Model used
All	10	1.04 (0.86-1.25)	0.0%	Fixed-effect
Type of supplements				
Vitamin A	3	1.06 (0.86-1.30)	13.1%	Fixed-effect
Vitamin B2	1	1.33 (0.30-5.91)	NA	NA
Vitamin C	3	1.00 (0.81-1.24)	0.0%	Fixed-effect
Vitamin E	6	1.00 (0.81-1.22)	0.0%	Fixed-effect
Folate	1	0.41 (0.02-9.76)	NA	NA
Beta-carotene	7	1.05 (0.87-1.27)	0.0%	Fixed-effect
Methodological quality				
High quality (score>3)	8	1.06 (0.87-1.28)	0.0%	Fixed-effect
Low quality (score≤3)	2	0.70 (0.31-1.61)	0.0%	Fixed-effect
Risk group for esophageal cancer				
High risk group	4	1.04 (0.85-1.28)	0.0%	Fixed-effect
Non-high risk group	6	1.01 (0.65-1.56)	0.0%	Fixed-effect

RR, relative risk; CI, confidence interval; NA, not applicable.

no efficacy of vitamin and antioxidant supplements in the prevention of esophageal cancer. Further, subgroup analyses by type of supplements, methodological quality, and risk group for esophageal cancer revealed no preventive efficacy of those supplements.

Our findings were inconsistent with those of previously published epidemiological studies and a meta-analysis of epidemiological studies, which had reported that people with the highest levels of antioxidant intake such as vitamin C or beta-carotene had an about 50% lower risk compared to those with lower levels of intake.[5]

There are several possible explanations for the inconsistent findings between observational epidemiological studies and RCTs. First, retrospective case-control studies are susceptible to recall and selection biases.[18] Esophageal cancer patients might recall wrongly their consumption of fruit and vegetables rich in vitamin and antioxidants. Even though they had have adequate intakes of fruit and vegetables long before their diagnosis of esophageal cancer, they might think incorrectly that they had consumed less foods because they had dyspepsia and loss of appetite due to cancer right before that diagnosis. Also, selection bias might affect the results because cases or controls are not representative of the population. Second, there are dif-

ferences in functions and components between natural vitamin or antioxidants and synthetic ones. For example, synthetic alpha-tocopherol (all-rac-alpha-tocopherol), which is composed of equal amounts of the 8 different stereoisomers of alpha-tocopherol, is different from its natural form (RRR-alpha-tocopherol).[19] Also, the human body absorbs and excretes natural and synthetic vitamin E differently, and those biological activities are different.[19,20] As for beta-carotene, experimental studies reported that beta-carotene might play a potential protective role against cancer initiation.[21] However, it may act as a prooxidant in the presence of chronic oxidative stress such as smoking; this may induce the oxidation of beta-carotene and DNA oxidative damage and finally lead to lung cancer.[18,22]

Third, eliminating reactive oxygen species by antioxidant supplementation might interfere with several essential defensive mechanisms like apoptosis and detoxification and unexpectedly increase mortality.[23] Last, antioxidant supplements might have interdependency and show those efficacy only when given in combination.[24]

There are several limitations in our study. First, we were unable to include several recent RCTs[25,26] because data for esophageal cancer were not reported. Second, the statistical power of the current meta-analysis is very low because the incidence of esophageal cancer is very low, compared with other types of common cancers. Further lager RCTs are needed to confirm our findings. Last, we were unable to apply our findings to healthy populations. Of 10 trials, only two trials involved general healthy populations, while the remaining trials involved a history of certain diseases or high risk populations for esophageal cancer.

In summary, unlike observational epidemiological studies, the current meta-analysis of RCTs found that there is no clinical evidence to support the efficacy of vitamin and antioxidant supplements in the prevention of esophageal cancer.

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Seung-Kwon Myung is responsible for the initial plan, study design, data screening, data selection, data interpretation, statistical analysis, manuscript drafting, and for conducting the study.

Hyo Jin Yang is responsible for data screening and data selection. SK Myung is the guarantor for this paper and has full responsibility for this study.

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