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Original Article

Incidence, Morbidity, and Mortality of Achalasia: A Nationwide, Population-Based Cohort Study in South Korea

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Background/Aims: Although an association between achalasia and esophageal cancer has been reported, whether achalasia confers a substantial increase in mortality is unknown. Moreover, the causes of death related to achalasia have not been investigated. We performed this nationwide, population-based cohort study on achalasia because no such study has been performed since the introduction of high-resolution manometry in 2008.

Methods: This study was performed using data extracted from the Korean National Health Insurance Service database, covering a 9-year period from 2009 to 2017. Control participants without a diagnostic code for achalasia were randomly selected and matched by sex and birth year at a case-to-control ratio of 1:4. Data on the cause of death from Statistics Korea were also analyzed.

Results: The overall incidence of achalasia was 0.68 per 100,000 person-years, and the prevalence was 6.46 per 100,000 population. Patients with achalasia (n=3,063) had significantly higher adjusted hazard ratio (aHR) for esophageal cancer (aHR, 3.40; 95% confidence interval [CI], 1.25 to 9.22; p=0.017), pneumonia (aHR, 2.30; 95% CI, 1.89 to 2.81; p<0.001), aspiration pneumonia (aHR, 3.92; 95% CI, 2.38 to 6.48; p<0.001), and mortality (aHR, 1.68; 95% CI, 1.44 to 1.94; p<0.001). Esophageal cancer carried the highest mortality risk (aHR, 8.82; 95% CI, 2.35 to 33.16; p=0.001), while pneumonia had the highest non-cancer mortality risk (aHR, 2.28; 95% CI, 1.31 to 3.96; p=0.004).

Conclusions: In this nationwide study, achalasia was associated with increased risk of mortality. Esophageal cancer and pneumonia were the most common comorbidities and the major causes of death in patients with achalasia. **(Gut Liver 2023;17:894-904)**

Key Words: Esophageal achalasia; Esophagus; Aspiration pneumonia; Esophageal neoplasms

INTRODUCTION

Achalasia is a motility disorder of the esophagus characterized by abnormal peristalsis and insufficient relaxation of the lower esophageal sphincter,[1] with symptoms such as dysphagia, regurgitation, vomiting, weight loss, and chest pain.[2] Epidemiologic studies on achalasia are limited owing to the rarity of this condition. The current literature shows that the worldwide incidence and prevalence of achalasia are approximately 1/100,000 and 10/100,000 person-years (py), respectively.[3,4] In South Korea, a study performed before the introduction of high-resolution manometry

reported that the incidence and prevalence of achalasia are 0.39/100,000 py and 6.29/100,000, respectively.[5]

The diagnosis of achalasia is made on the basis of findings of esophagogastroduodenoscopy, barium esophagography, esophageal manometry, and recently introduced endoflip.[6] Different treatment modalities are available, ranging from medical to surgical or endoscopic treatment.[3,7,8] Importantly, the accuracy of achalasia diagnosis was substantially improved by the introduction of high-resolution manometry in 2008, which accordingly has led to an increased incidence of achalasia compared with that during the era of conventional manometry.[9] However, the long-term prognosis after the diagnosis and treatment of achalasia has rarely been investigated. Several studies have suggested an association between achalasia and esophageal cancer[10-12] and lower respiratory tract infection.[12] Therefore, a long-term study using a nationwide database of patients with achalasia diagnosed using high-resolution manometry is needed to accurately assess the real-world incidence and prevalence of achalasia.

South Korea is suitable country for conducting nationwide epidemiologic studies because it provides a national health-care system covering 97.2% of the population,[13] as well as a well-controlled computerized medical record system and easy access to medical institutions. Moreover, doctors in South Korea use the diagnostic codes of the 10th edition of the International Classification of Diseases (ICD-10) to submit claims to the National Health Insurance Review and Assessment Service. Therefore, in this study, we investigated the incidence, prevalence, and associated morbidity and mortality rates of achalasia by using the National Health Insurance Service (NHIS) database of South Korea.

MATERIALS AND METHODS

1. Data source

Data from the Korean NHIS were used in this study. The NHIS is managed by the South Korean government and consists of the National Health Insurance and Medical Aid programs that cover the entire national population. The NHIS database has been available since 2002 and provides information including insurance type, income, sex, age, medical diagnosis, and details of prescriptions and medical procedures provided. The medical institution database provides information about each medical care facility. The details of this process and a provision guide are available at https://nhiss.nhis.or.kr/bd/ab/bdaba032eng.do.

Furthermore, the date and cause of death could be linked to death certificates collected by Statistics Korea (Ministry of Economy and Finance, Republic of Korea). Information about mortality and cause of death was available for all participants in our cohort. The cause of death was classified according to ICD-10 codes, as provided by Statistics Korea. Diseases or conditions directly leading to death were considered specific causes of death.

The Institutional Review Board of Asan Medical Center approved this study (IRB number: 2020-1251) and waived the need for informed consent. The study was performed according to the principles of the Declaration of Helsinki.

2. Study population

The NHIS database (2002 to 2018) was searched to identify all patients with an ICD-10 diagnostic code of K22.0 (achalasia) after 2008. Patients who were diagnosed at a secondary or higher medical institution using an upper gastrointestinal series (national health insurance payment code HA010, HA011, or HA012), esophagography (HA040), or esophageal manometry (E7030 or E7031) were considered to have a diagnosis of true achalasia. We included only patients diagnosed with achalasia after 2008 because (1) the introduction of high-resolution manometry in 2008 substantially improved the diagnostic accuracy of achalasia;[14] (2) the diagnostic codes were reorganized to provide more consistent information; and (3) we sought to ensure that an observation period was available before the diagnosis of achalasia was made. Therefore, among the 3,534 patients who were diagnosed with achalasia between 2009 and 2017, 423 who were previously diagnosed with achalasia in 2002 to 2008 were excluded. Additionally, the following patients were excluded: those whose demographic data were not linked (n=9) and those diagnosed with esophageal cancer (n=15), stomach cancer (n=12), or lung cancer (n=10) prior to achalasia diagnosis or within 1 year of the achalasia diagnosis. Finally, a total of 3,065 patients were analyzed (Supplementary Fig. 1). Control participants who had never been diagnosed with achalasia were randomly selected from the NHIS database and matched by sex and birth year at a case-to-control ratio of 1:4.

3. Validation of NHIS data

The NHIS database is considered accurate because all medical institutions in South Korea are registered in this single database and use uniform disease codes. Nevertheless, we further confirmed its accuracy. We compared the number of patients with achalasia for whom claims were sent to the Health Insurance Review and Assessment Service in Songpa-Kangdong district, an area southeast of Seoul, South Korea, with the number of patients diagnosed with achalasia at Asan Medical Center, a tertiary medical institution located in Songpa-Kangdong district. The same

operational definition of achalasia used in this study was used to compare the data. During the last 3 years of data collection (from 2015 to 2017), the number of patients with achalasia for whom claims were sent to the Health Insurance Review & Assessment Service was compared with the number of patients diagnosed with achalasia using manometry at Asan Medical Center. Therefore, we confirmed that the NHIS data reflect real-world data.

4. Outcomes

Cancer diagnosis was confirmed using ICD-10 cancer codes at the primary and secondary diagnoses and contained a cancer confirmation code (V027, V193, or V194). All ICD-10 cancer codes (from C00 to C97) were assessed, particularly esophageal cancer (C15), stomach cancer (C16), and lung cancer (C34), which were separately evaluated. Other outcomes of interest in this study included aspiration pneumonia (J690), ischemic heart disease (I20–I25), stroke (I63, I64, I693, I694, and G459), heart failure (I50), and peripheral vascular disease (I739 and I7388). Additionally, pneumonia (J13–18, J690, and J189) codes included aspiration pneumonia (J690), overall pneumonia was analyzed as an outcome, and among them, aspiration pneumonia, which was more strongly correlated in achalasia patients, was analyzed separately. To increase the validity of the diagnostic codes for the outcomes, only patients who were hospitalized at the time of the diagnosis were considered to have a definitive diagnosis and only their data were included. The detailed definitions of the ICD-10 codes used in this study are provided in Supplementary Table 1.

5. Covariates or potential confounders

From the baseline characteristics of the patients, comorbidities were identified when insurance claims were made more than twice within 1 year, with ICD-10 codes including hypertension (I10–I13 and I15), diabetes mellitus (E10–E14), or dyslipidemia (E78) and the Charlson Comorbidity Index (CCI).[15]

6. Statistical analysis

Baseline characteristics are presented as numbers and percentages for categorical variables. The balance in the distribution of baseline characteristics between patients with achalasia and matched controls was quantified using the standardized difference of the mean (STD), with an STD of <0.1 indicating a fair balance of confounders between the matched groups. The prevalence and incidence of achalasia were calculated by assuming an exact Poisson distribution. The incident rate ratio was calculated by comparing calendar years. The time to outcome was estimated using the Kaplan–Meier method. The risk of each outcome was estimated as hazard ratios (HRs) with 95% confidence intervals (CIs) using the Cox regression models, with robust standard errors that accounted for the clustering of matched pairs. Multivariate analysis was performed to adjust for age, health insurance type, and comorbidities. Values of $p<0.05$ were considered statistically significant. All statistical analyses were performed using the SAS Enterprise Guide software version 7.1 (SAS Institute Inc., Cary, NC, USA) or R statistical software version 4.0.3 (R Foundation Inc., Vienna, Austria, http://cran.r-project.org/).

RESULTS

A total of 3,063 patients with achalasia and 11,083 matched controls were included in this study. The mean follow-up duration was 4.83 py (standard deviation, 2.69) and 5.02 py (standard deviation, 2.66) for the achalasia and control groups, respectively. The patients' demographic data are shown in Table 1. The achalasia group was older (51.7±19.3 years vs 49.6±18.8 years; STD, 0.108) than the control group, and the groups were matched to within 5 years of age. No significant intergroup differences were observed in sex, diabetes, health insurance type, or income quintile. Hypertension (28.4% vs 20.9%; STD, 0.177), dyslipidemia (24.0% vs 16.0%; STD, 0.201), and higher CCI values were more common in the achalasia group.

1. Incidence and prevalence of achalasia

The incidence and prevalence of achalasia were analyzed using the NHIS data. The overall incidence of achalasia per 100,000 population in 1 year during the study period was 0.67 (0.65 to 0.70). The prevalence of achalasia was 6.46 (6.24 to 6.68) per 100,000 population. The incidence of achalasia increased during the study period from 2009 to 2017 (incident rate ratio, 1.05; 95% CI, 1.03 to 1.07; $p<0.001$). The annual incidence of achalasia is shown in Table 2.

2. Morbidity outcomes of the matched achalasia and control groups

After adjusting for potential confounding factors, we found that esophageal cancer was more common in the achalasia group than in the control group (adjusted HR, 3.40; 95% CI, 1.25 to 9.22; $p=0.017$). Other conditions that were more common in the achalasia group included pneumonia (adjusted HR, 2.30; 95% CI, 1.89 to 2.81; $p<0.001$), aspiration pneumonia (adjusted HR, 3.92; 95% CI, 2.38 to 6.48; $p<0.001$), and ischemic heart disease (adjusted

Table 1. Characteristics of the Achalasia and Control Groups Derived from National Health Insurance Service Data

Variable	Achalasia group (n=3,063)	Control group (n=11,083)	STD
Age, yr	51.7±19.3	49.6±18.8	0.108
Female sex	1,614 (53.0)	6,004 (54.2)	0.030
Charlson Comorbidity Index			
0	1,301 (42.5)	7,459 (67.3)	0.529
1 to <3	1,252 (40.9)	2,735 (24.7)	
3 to <5	336 (11.0)	632 (5.7)	
≥5	174 (5.7)	257 (2.3)	
Hypertension	869 (28.4)	2,321 (20.9)	0.177
Diabetes mellitus	413 (13.5)	1,151 (10.4)	0.095
Dyslipidemia	736 (24.0)	1,773 (16.0)	0.201
Insurance type			
National Health Insurance	2,892 (94.4)	10,651 (96.1)	−0.085
Medical Aid	171 (5.6)	432 (3.9)	
Income quintile, %			
Unknown	234 (7.6)	675 (6.1)	0.071
≤20	395 (12.9)	1,556 (14.0)	
>20 to 40	397 (13.0)	1,640 (14.8)	
>40 to 60	518 (16.9)	1,878 (16.9)	
>60 to 80	641 (20.9)	2,293 (20.7)	
>80 to 100	878 (28.7)	3,041 (27.4)	

Data are presented as mean±SD or number (%).
STD, standardized difference of the mean.

Table 2. Incidence of Achalasia by Year

Index year	No. of patients	Total population	Incidence	95% CI
2009	306	49,656,756	0.62	0.55–0.69
2010	302	49,879,812	0.61	0.54–0.68
2011	278	50,111,476	0.55	0.49–0.62
2012	308	50,345,325	0.61	0.55–0.68
2013	315	50,558,952	0.62	0.56–0.70
2014	333	50,763,158	0.66	0.59–0.73
2015	354	50,951,719	0.69	0.62–0.77
2016	423	51,112,972	0.83	0.75–0.91
2017	446	51,230,704	0.87	0.79–0.96
Overall	3,065	454,610,872	0.67	0.65–0.70

CI, confidence interval.

HR, 1.68; 95% CI, 1.29 to 2.19; p<0.001). The incidence of peripheral vascular disease, heart failure, stroke, stomach cancer, and other cancers (excluding esophageal cancer) did not significantly differ between the two groups. The median time from achalasia diagnosis to esophageal cancer diagnosis was 2.95 years (interquartile range, 1.40 to 4.44 years). The details of the morbidity outcomes are provided in Table 3, and the cumulative incidence plots of time from achalasia diagnosis to esophageal cancer and aspiration pneumonia diagnoses are shown in Fig. 1.

3. Mortality in patients with achalasia

There were 279 deaths in 14,805 py in the achalasia group compared with 468 deaths in 55,601 py in the control group (crude HR, 2.24; 95% CI, 1.96 to 2.56; p<0.001). After adjusting for age, health insurance type, and CCI, the mortality rate remained significantly higher in the achalasia group (adjusted HR, 1.60; 95% CI, 1.37 to 1.86; p<0.001). The cumulative incidence plots of time from achalasia diagnosis to death are shown in Fig. 2. In the achalasia group, esophageal cancer (crude HR, 11.19; 95% CI, 3.04 to 41.19; p<0.001) conferred the highest risk of death, whereas pneumonia (crude HR, 3.27; 95% CI, 1.96 to 5.45; p<0.001) conferred the highest risk of non-cancer death. The risk was maintained after adjusting for age, health insurance type, and CCI (esophageal cancer: adjusted HR, 8.82; 95% CI, 2.35 to 33.16; p=0.001; pneumonia: adjusted HR, 2.28; 95% CI, 1.31 to 3.96; p=0.004) (Table 4).

DISCUSSION

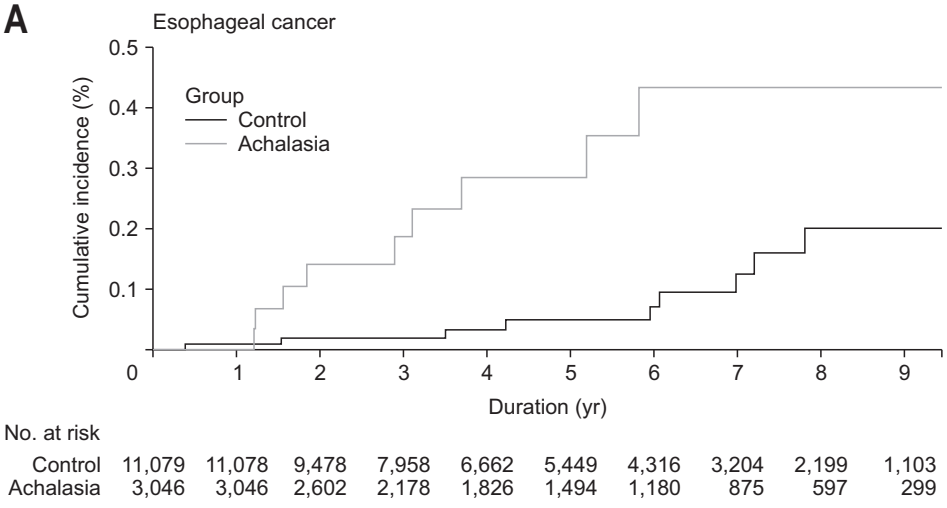
In this nationwide, population-based cohort study performed in South Korea, the incidence of achalasia was 0.68/100,000 py and showed an increasing trend during the study period (2009 to 2017). The incidence of esophageal cancer was higher in the achalasia group than in the

Table 3. Disease Outcomes of the Achalasia and Control Groups

Disease	Total	No. of cases	Total py	IR/1,000 py	95% CI	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Esophageal cancer						3.65 (1.45–9.20)	0.006	3.40 (1.25–9.22)	0.017
Case	3,046	9	15,622	0.58	0.26–1.09				
Control	11,079	9	56,998	0.16	0.07–0.30				
Cancers other than esophageal cancer						1.43 (1.17–1.74)	0.001	1.21 (0.97–1.49)	0.09
Case	2,855	132	14,360	9.19	7.69–10.90				
Control	10,648	347	53,852	6.44	5.78–7.16				
Stomach cancer						0.89 (0.49–1.64)	0.715	0.69 (0.37–1.28)	0.24
Case	3,025	13	15,536	0.84	0.45–1.43				
Control	11,006	53	56,524	0.94	0.70–1.23				
Lung cancer						1.29 (0.75–2.23)	0.363	1.11 (0.63–1.95)	0.71
Case	3,035	17	15,575	1.09	0.64–1.75				
Control	11,056	48	56,756	0.85	0.62–1.12				
Pneumonia						2.87 (2.38–3.46)	<0.001	2.30 (1.89–2.81)	<0.001
Case	2,820	200	13,839	14.45	12.52–16.60				
Control	10,775	275	54,683	5.03	4.45–5.66				
Aspiration pneumonia						5.27 (3.29–8.43)	<0.001	3.92 (2.38–6.48)	<0.001
Case	3,041	43	15,460	2.78	2.01–3.75				
Control	11,074	30	56,920	0.53	0.36–0.75				
Ischemic heart disease						2.05 (1.59–2.66)	<0.001	1.68 (1.29–2.19)	<0.001
Case	2,842	85	14,356	5.92	4.73–7.32				
Control	10,779	159	55,167	2.88	2.45–3.37				
Stroke						1.60 (1.23–2.09)	<0.001	1.17 (0.89–1.55)	0.26
Case	2,958	76	15,003	5.07	3.99–6.34				
Control	10,861	175	55,357	3.16	2.71–3.67				
Heart failure						1.70 (1.29–2.24)	<0.001	1.34 (1.00–1.79)	0.05
Case	2,896	70	14,713	4.76	3.71–6.01				
Control	10,809	154	55,041	2.80	2.37–3.28				
Peripheral vascular disease						1.88 (1.27–2.78)	0.002	1.40 (0.94–2.10)	0.10
Case	3,022	39	15,460	2.52	1.79–3.45				
Control	11,035	76	3,022	25.15	19.81–31.48				

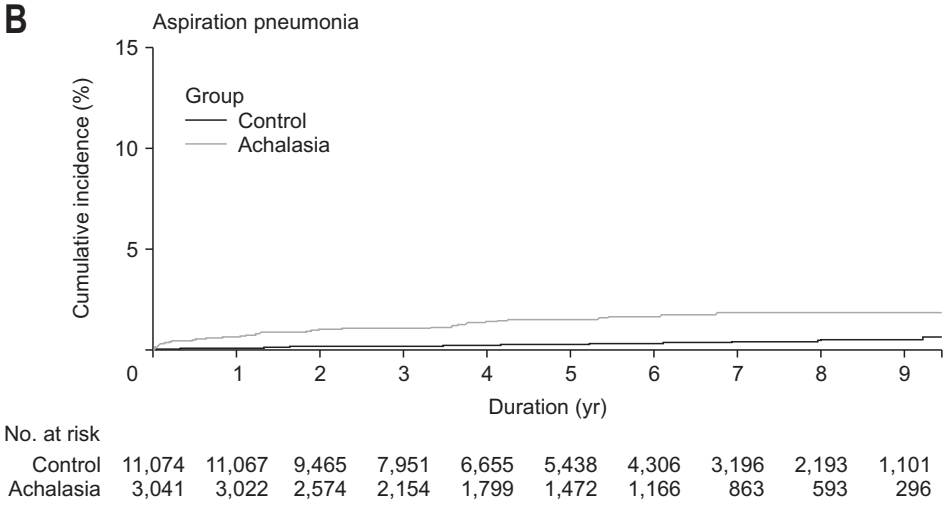
py, person-years; IR, incidence rate; CI, confidence interval; HR, hazard ratio.

matched control group, whereas the incidence of other cancers did not significantly differ between groups. The incidence of aspiration pneumonia was also higher in the achalasia group; however, with the exception of ischemic heart disease, the incidence of other comorbidities was not significantly different between the two groups. Achalasia



No. at risk

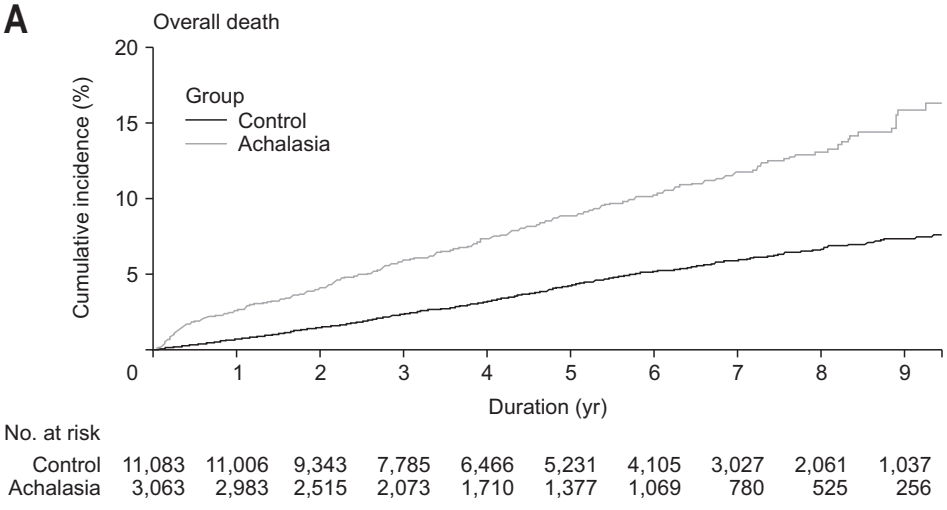
Control	11,079	11,078	9,478	7,958	6,662	5,449	4,316	3,204	2,199	1,103
Achalasia	3,046	3,046	2,602	2,178	1,826	1,494	1,180	875	597	299



No. at risk

Control	11,074	11,067	9,465	7,951	6,655	5,438	4,306	3,196	2,193	1,101
Achalasia	3,041	3,022	2,574	2,154	1,799	1,472	1,166	863	593	296

Fig. 1. Cumulative incidence plot of time from achalasia diagnosis to esophageal cancer and aspiration pneumonia diagnoses. (A) Cumulative incidence plot of time from achalasia diagnosis to esophageal cancer diagnosis. (B) Cumulative incidence plot of time from achalasia diagnosis to aspiration pneumonia diagnosis.



No. at risk

Control	11,083	11,006	9,343	7,785	6,466	5,231	4,105	3,027	2,061	1,037
Achalasia	3,063	2,983	2,515	2,073	1,710	1,377	1,069	780	525	256

Fig. 2. Cumulative incidence plot of time from achalasia diagnosis to death. (A) Cumulative incidence of overall death in the control and achalasia groups. (B) Cumulative incidence of cancer-related death in the control and achalasia groups. (C) Cumulative incidence of esophageal cancer-related death in the control and achalasia groups. (D) Cumulative incidence of pneumonia-related death in the control and achalasia groups.

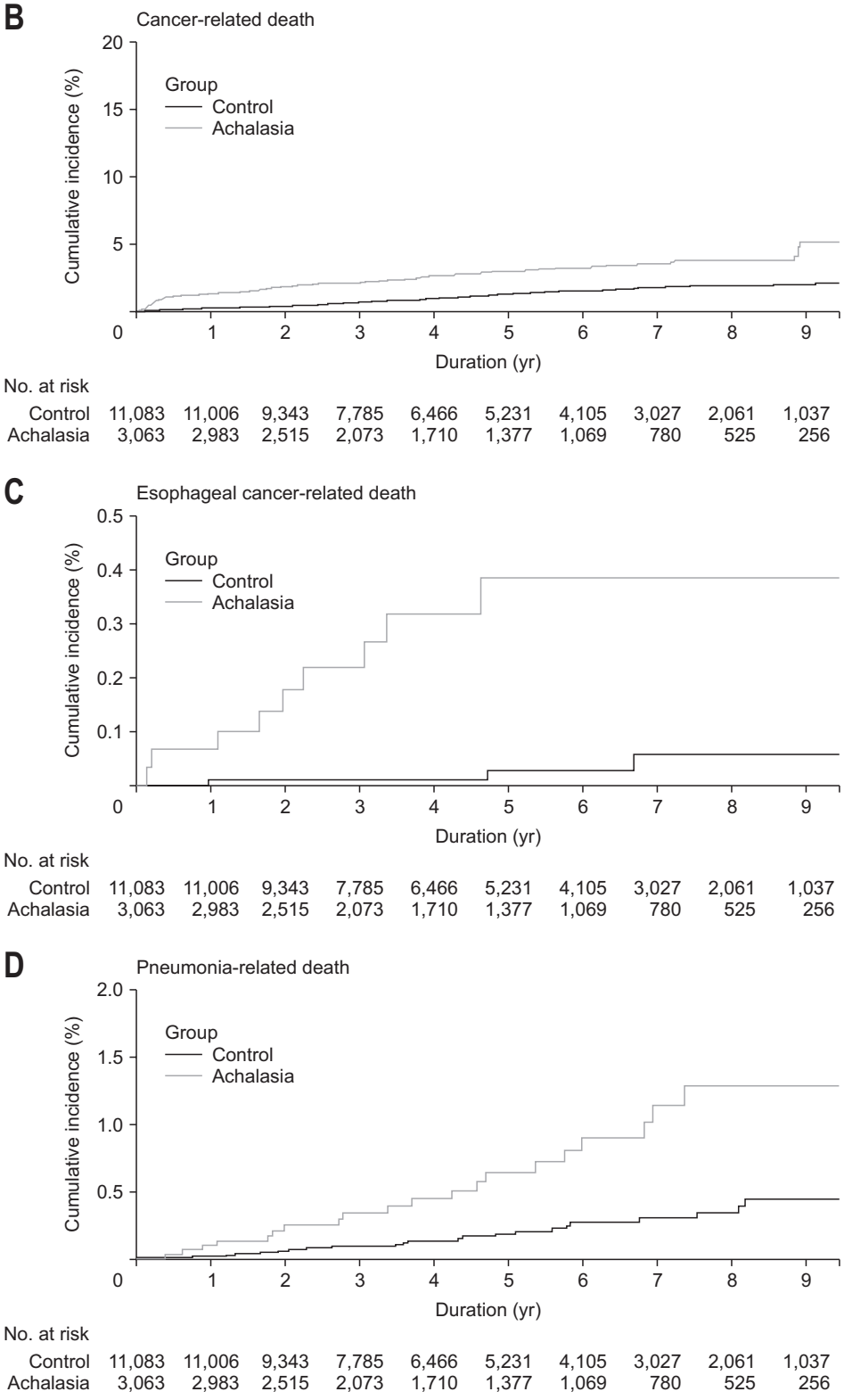


Fig. 2. Continued.

was associated with a high mortality rate, and the association remained statistically significant after adjusting for possible confounders.

Epidemiologic data on achalasia are limited because of the rarity of this condition. Recent population-based studies reported that the incidence and prevalence of achalasia were 1.63/100,000 py and 10.82/100,000 in Canada,[16] 1.53/100,000 py and 27.1/100,000 in the United King-

Table 4. Mortality in the Achalasia and Control Groups

Variables	Total	No. of deaths	Total py	IR/100 py	95% CI	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
All-cause death						2.24 (1.96–2.56)	<0.001	1.60 (1.37–1.86)	<0.001
Case	3,063	279	14,805	1.88	1.67–2.12				
Control	11,083	468	55,601	0.84	0.77–0.92				
Cancer-related death						2.54 (1.94–3.33)	<0.001	1.84 (1.38–2.45)	<0.001
Case	3,063	89	14,805	0.60	0.48–0.74				
Control	11,083	131	55,601	0.24	0.20–0.28				
Esophageal cancer-related death						11.19 (3.04–41.19)	<0.001	8.82 (2.35–33.16)	0.001
Case	3,063	9	14,805	0.06	0.03–0.12				
Control	11,083	3	55,601	0.01	0.00–0.02				
Lung cancer-related death						2.53 (1.45–4.40)	0.001	1.68 (1.00–2.80)	0.05
Case	3,063	21	14,805	0.14	0.09–0.22				
Control	11,083	31	55,601	0.06	0.04–0.08				
Gastric cancer-related death						2.79 (1.18–6.60)	0.02	1.89 (0.82–4.31)	0.135
Case	3,063	9	14,805	0.06	0.03–0.12				
Control	11,083	12	55,601						
Pneumonia-related death						3.27 (1.96–5.45)	<0.001	2.28 (1.31–3.96)	0.004
Case	3,063	25	14,805	0.17	0.11–0.25				
Control	11,083	29	55,601	0.05	0.03–0.07				

py, person-years; IR, incidence rate; CI, confidence interval; HR, hazard ratio.

dom,[12] 0.81 to 1.37/100,000 py and 7.0/100,000 in Japan,[17] and 0.39/100,000 py and 6.29/100,000 in South Korea,[5] respectively. The incidence and prevalence of achalasia in the current study are higher than the previously reported values based on conventional manometry in South Korea;[5] the discrepancy between the two studies is likely due to the fact that whereas our nationwide study examined patients with achalasia diagnosed at secondary or tertiary medical centers based on high-resolution manometry data, the previous study was based on achalasia diagnosed by conventional manometry. Meanwhile, the incidence and prevalence of achalasia in this study are lower than those reported in Western countries, and the reason for this difference should be examined in a further study targeting patients with achalasia.

The association between achalasia and esophageal cancer has been reported previously, with squamous cell carcinoma being recognized as the dominant pathology. The mechanism of carcinoma development due to achalasia is presumed to be related to poor esophageal emptying, food stasis, and inflammation.[1] A recent study reported that the interval between the diagnosis of achalasia and the development of esophageal cancer is approximately 15 years.[12] The risk of esophageal cancer was reported to be higher in patients with achalasia than in the general population, by 11 times in Sweden,[10] 5 times in the United Kingdom,[12] and 8 times in Japan.[17] In this study, the risk of esophageal cancer was 3.4 times higher in patients with achalasia than in controls after adjusting for potential confounding factors, and the median time to the esophageal cancer diagnosis was 2.95 years. Although the pathology of esophageal cancer could not be determined in this study, it is presumed to be mostly squamous cell cancer considering that >90% of esophageal cancer cases in South Korea are squamous cell carcinoma.[18,19] A possible reason for the short median time to the diagnosis of esophageal cancer is that upper endoscopy is inexpensive and is performed every 2 years in South Korea as a part of the national cancer screening program, thus enabling the early detection and treatment of esophageal cancer. The national stomach cancer screening program is implemented in South Korea because stomach cancer is one of the leading causes of cancer in South Korea, and the South Korean government thus recommends regular upper endoscopy and covers 90% of the cost. In fact, in this study, six of the nine patients with achalasia who developed esophageal cancer survived during the study period or died of other causes (e.g., hepatocellular carcinoma and prostate cancer).

A recent population-based study conducted in the United Kingdom reported that aspiration pneumonia is 13.4 times more common in patients with achalasia than in the general population.[12] This association can be explained by poor esophageal emptying, which is the same mechanism that likely contributes to esophageal cancer development. In this study, patients diagnosed with achalasia had a 3.93 times higher risk of developing aspiration pneumonia, which is a lower value than that reported in the previous U.K.-based study. However, the two studies cannot be directly compared because we retrospectively reviewed the disease codes entered by physicians and strictly established the diagnostic criteria of aspiration pneumonia (coexistence of diagnostic code and admission). Despite the difference in the degree of increased risk, our study supports the notion that patients with achalasia have an increased risk of aspiration pneumonia.

Previous studies on the risk of mortality in patients with achalasia showed discrepant results. A case series from a tertiary center, published in 2008, showed that patients with achalasia had an average life expectancy.[20] In contrast, a population-based study in 2019 reported that patients with achalasia had a 1.37 times higher risk of mortality.[12] Such discrepancy is likely due to the differences in the study design (i.e., single-center case series vs population-based study) and the increase in the accuracy of achalasia diagnosis after the introduction of high-resolution manometry in 2008. Our study, which examined the largest population-based cohort of patients with achalasia, confirmed the high risk of death in these patients. We also found that esophageal cancer and pneumonia were the most common causes of death in patients with achalasia. The high mortality rate associated with achalasia might have been affected by the high prevalence of hypertension and dyslipidemia and the low body mass index in patients with achalasia; however, the risk of death due to esophageal cancer and pneumonia in patients with achalasia was still significantly high after adjusting for possible confounders. Therefore, monitoring and managing esophageal cancer and pneumonia in patients with achalasia are the most important factors for increasing their life expectancy.

The strength of this study is that the results represent the general population of South Korea because the study data were obtained from the NHIS, which is the single compulsory national health insurance system in South Korea. Furthermore, the cause of death in each individual could be determined by linking data from Statistics Korea. Therefore, to our knowledge, this is the first study to link cause-of-death data in patients with achalasia.

This study had several limitations that warrant discussion. First, although we were able to investigate esophageal cancer as a cause of death, we could not investigate aspiration pneumonia as a specific cause of death because the NHIS database contains the code for pneumonia, rather

than a more specific code for aspiration pneumonia. Second, variables such as body mass index, smoking status, and alcohol consumption may be related to other diseases such as ischemic heart diseases and other malignancies. To overcome this limitation, we used CCI, which could be calculated using the NHIS data, as an adjustment variable. After adjustment with CCI, other common disease outcomes did not show significant associations to achalasia. Therefore, we believe that the observed correlation between esophageal cancer and achalasia is valid. Third, the treatment methods for achalasia were not analyzed in this study because data on peroral esophageal myotomy, which is performed in most patients, have only recently been entered into the NHIS database. Therefore, the differences in mortality and morbidity rates according to treatment modality remain unknown. Additional long-term studies are needed to further investigate this issue. Fourth, esophageal cancer could not be classified according to the subtype (e.g., squamous cell carcinoma, adenocarcinoma) or anatomical location because the NHIS database lacked the relevant information. Additionally, we could not check and show the history of drug use such as proton pump inhibitor and national cancer screening esophagogastroduodenoscopy, and whether there is any difference between the control group and the achalasia group. Lastly, not all achalasia cases in this study had been diagnosed using manometry, and future studies may benefit from solely including cases that were diagnosed using high-resolution manometry that provides higher diagnostic sensitivity than esophagogastroduodenoscopy or esophagogram.

In conclusion, this is the first study to examine the cause of death related to achalasia by analyzing a nationwide, population-based database after the introduction of high-resolution manometry. We reported the increased mortality and key morbidities associated with achalasia. Specifically, esophageal cancer and pneumonia were significantly related to achalasia and were the most common causes of death in our cohort.

CONFLICTS OF INTEREST

J.Y.A. and H.J.K. are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: K.W.J., H.J.K., G.H.K., H.P. Data acquisition: J.M.L., B.E.L., Y.W.M., J.H.K., H.K.N., J.Y.A., J.H.L., K.W.J., D.H.K., H.J.S., K.D.C., G.H.L., H.Y.J. Data analysis and interpretation: M.J.K., Y.J.K., G.H.K. Drafting of the manuscript: K.W.J., H.J.K., G.H.K. H.P. Critical revision of the manuscript for important intellectual content: K.W.J., H.J.K., G.H.K., H.P. Statistical analysis: M.J.K., Y.J.K. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl220334.

DATA AVAILABILITY STATEMENT

This study used data from the National Health Insurance Service (NHIS) customized health information database (NHIS-2020-1-218) provided by the Korean NHIS.

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