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Association Between Pneumonia and Chronic Otitis Media: A Nested Case-Control Study Using a National Health Screening Cohort

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ABSTRACT

Background: Pneumonia and chronic otitis media (COM) share a common pathophysiological mechanism in terms of respiratory infection and inflammation, but the epidemiologic association between the 2 diseases has not been investigated. We investigated the association between an event of COM and previous events of pneumonia in a national cohort.

Methods: Data from the Korean National Health Insurance Service-Health Screening Cohort were collected from 2002 to 2015. A 1:4 stratified cohort matched for age, sex, income, and residence region composing the COM group (n=23,436) and a control group (n=93,744) was selected. The crude and adjusted odds ratios (ORs) of pneumonia occurring before the index date for COM were analyzed using a conditional logistic regression model. In addition, ORs of the number of diagnoses of pneumonia (≥5 times vs. <5 times) for COM were analyzed.

Results: The incidence of pneumonia (9.3%) was significantly higher (p<0.001) in the COM group than in the control group (7.2%). The ORs of pneumonia were significantly higher in the COM group than in the control group. Pneumonia (adjusted OR=1.31, 95% confidence interval [CI]=1.25–1.38, p<0.001) increased the ORs for COM in all ages and gender. Pneumonia being diagnosed ≥5 times before the index date showed higher ORs (adjusted OR=1.34, 95% CI=1.20–1.49, p<0.001) for COM than pneumonia being diagnosed <5 times.

Conclusions: Our population-based nationwide cohort study indicates that diagnosis of pneumonia was significantly associated with an increased incidence of COM.

Introduction

Chronic otitis media (COM) refers to the presence of tympanic membrane perforation and otorrhea, accompanied by irreversible chronic inflammation in the middle ear and mastoid cavity. It is also characterized by accumulation of middle ear effusion without specific signs of inflammation, persisting for more than 3 months. COM presents the concepts of chronic suppurative otitis media, characterized by perforation of the tympanic membrane and recurrent or persistent otorrhea from the middle ear, and chronic otitis media with effusion, in which mucoid and serous effusion are observed in the middle ear cavity without signs of infection for more than 3 months. The prevalence of COM in South Korea was 3.8% according to the Korean National Health and Nutrition Examination Survey in 2012 (Chung et al., 2016), and the prevalence of COM is declining worldwide due to the improvement in socioeconomic conditions, the use of antibiotics, improved nutritional and sanitation conditions, and increased access to medical facilities (Akinpelu et al., 2008). Various conditions, such as dysfunction of the eustachian tube and chronic rhinosinusitis that can cause mechanical obstruction of ventilation routes, are known to be associated with the occurrence of COM (Hong et al., 2017; Lou and Lou, 2018; Verhoeff et al., 2006).

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Recently, middle ear diseases, including COM, have been recognized as respiratory tract diseases beyond the pathophysiological concepts of ventilation dysfunction, with recurrent infection that occurs from anatomically adjacent structures such as the middle ear, mastoid cavity, and eustachian tube. Infection in the respiratory tract can cause microbial dysbiosis, which can affect the composition of the microbial community of the paranasal sinus, oral cavity, and nasopharynx(Hauptmann and Schaible, 2016, Welp and Bomberger, 2020). Airflow limitation, hypoxemia, and an increase in inflammatory cytokine levels due to recurrent respiratory inflammation not only lead to tissue remodeling of the respiratory mucosa but also decrease the mucociliary clearance and oxygen availability to the mucosa covering the eustachian tube, middle ear, and mastoid air cells (Alshukry et al., 2020). However, studies on the relationship between respiratory tract diseases and otitis media have mainly been conducted targeting upper respiratory tract (URT) diseases such as bronchitis and asthma, eosinophilic otitis media, and otitis with effusion in children (Kim et al., 2021; Seo et al., 2020; Wine and Alper, 2012).

Pneumonia is an acute infection of the lower respiratory tract (LRT) and lung parenchyma that affects 450 million people per year (Troeger et al., 2018). It is a prevalent infectious disease worldwide, with approximately 4 million deaths annually and is a significant social and economic burden due to its high mortality and morbidity (Vos et al., 2020). As bacterial and viral inflammatory conditions of the LRT, such as bronchiolitis and pneumonia, interfere with mucin-bacterial interactions on the URT or nasopharynx epithelial surface (especially in children), they increase the burden of pathogenic bacteria, leading to otitis media and rhinosinusitis (Bernstein and Reddy, 2000). In addition, recently, using culture-independent techniques through next-generation sequencing, a complex community of microorganisms has been identified in the respiratory tract, and the possibility of an association between pneumonia and various diseases has been suggested on the basis of impairment of the host immune mechanism (Pendleton et al., 2017, Teo et al., 2015). However, despite the pathophysiological mechanism based on the concept of 1 airway, most studies have focused on the association between URT diseases and otitis media in children, and there have been no studies on the epidemiological association between pneumonia and COM in adults.

We hypothesized that pneumonia might affect COM. The goal of the present study was to evaluate whether subjects diagnosed with COM were more likely to have previous events of pneumonia by conducting a nested case-control study using population data from a national health check-up cohort.

Materials and Methods

Study Population and Participant Selection

A detailed description of the Korean National Health Insurance Service-Health Screening Cohort data has been described elsewhere (Kim et al., 2019). Participants with COM were selected from 514,866 participants with 615,488,428 medical claim codes (n = 42,099) between January 2002 and December 2015. The control group was taken from all participants who were not diagnosed with COM (n = 472,767). To measure the number of patients diagnosed with pneumonia in the past 3 years, we excluded participants with COM who were diagnosed between 2002 and 2005 (n=18,663). Among control participants, we excluded those who were diagnosed with ICD-10 codes H65 (nonsuppurative otitis media), H66 (suppurative and unspecified otitis media), and H67 (otitis media in diseases classified elsewhere) (n=72,340).

Participants with COM were 1:4 matched with control participants for age, gender, income, and residence region. To minimize selection bias, the control participants were selected by random number order. The index date of each participant with COM was set as the time of treatment for COM. The index date of control participants was set as the index date of their matched participants with COM. Therefore, each matched participant with COM and control participants had the same index date. During the matching process, 306,683 control participants were excluded. Finally, 23,436 participants with COM were 1:4 matched with 93,744 control participants (Fig. 1).

Exposure (the Frequency of Pneumonia)

Pneumonia was defined if the participant was diagnosed with ICD-10 codes J12 to J18 and underwent chest X-ray or chest CT.

For the sensitivity analyses, the number of patients diagnosed with pneumonia was classified as <5 times and ≥5 times by period (before index dates, for 1 year before index dates, for 2 years before index dates, and for 3 years before index dates).

Outcome (COM)

Following our previous study (Choi et al., 2017), (COM was defined if participants were diagnosed with the following ICD-10 codes ≥2 times: chronic serous otitis media (H65.2), chronic mucoid otitis media (H65.3), other chronic nonsuppurative otitis media (H65.4), unspecified nonsuppurative otitis media (H65.9), chronic tubotympanic suppurative otitis media (H66.1), chronic atticoantral suppurative otitis media (H66.2), other chronic suppurative otitis media (H66.3), and unspecified suppurative otitis media (H66.4).

Covariates

Age groups were divided into 5-year intervals: 40–44, 45–49, 50–54…, and 85+ years old (total of 10 age groups). Income groups were classified into 5 classes (class 1 [lowest income]-5 [highest income]). The region of residence was grouped into urban and rural areas, following our previous study (Kim et al., 2020a). Tobacco smoking, alcohol consumption, and obesity based on the body mass index (BMI, kg/m^2) were categorized as previously reported (Kim et al., 2020b, Organization, 2000). The systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose level, and total cholesterol level were measured. Missing BMI (n=1, 0.001%), fasting blood glucose level (n=1, 0.001%), and total cholesterol level (n=2, 0.002%) values were replaced by the mean values of each variable from the final selected participants. The Charlson comorbidity index (CCI) has been used widely to measure disease burden based on 17 comorbidities (Quan et al., 2011).

Statistical Analyses

Chi-square tests were used to compare the general characteristics between the COM and the control groups.

To analyze the odds ratio (OR) of pneumonia occurring before COM and the OR of the number of patients diagnosed with pneumonia by period, and conditional logistic regression analysis was used in the matched groups for age, gender, income, and residence region. In these analyses, crude (simple) and adjusted models (obesity, smoking status, alcohol consumption, SBP, DBP, fasting blood glucose level, total cholesterol level and CCI score) were used. The 95% confidence interval (CI) was calculated. In these analyses, age, gender, income, and residence region were stratified. For the subgroup analyses, we divided the participants by age and gender (<60 years old and ≥ 60 years old, men and women) to confirm these associations according to age and gender. The division of the

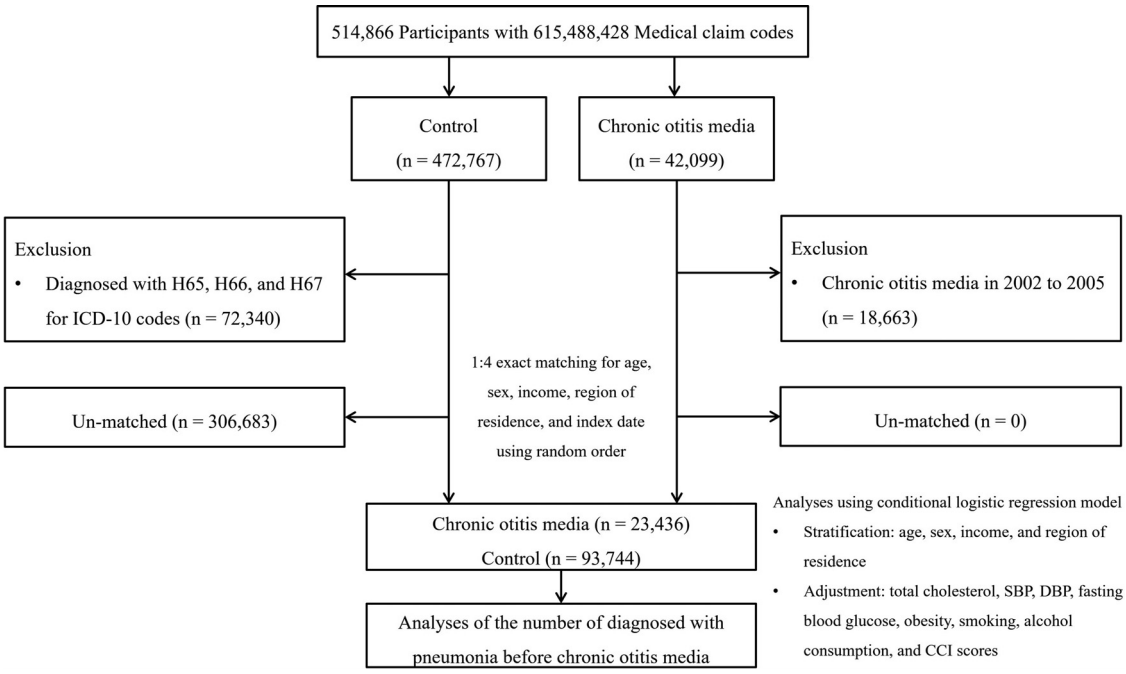

Figure 1. A schematic illustration of the participant selection process that was used in the current study. Of a total of 514,866 participants, 23,436 chronic otitis media patients were matched with 93,744 control participants based on age, sex, level of income, and region of residence.

age groups was determined by the median value of the total number of participants. We further analyzed the OR of the number of patients diagnosed with pneumonia (per 5 cases of pneumonia) by period for COM (S1 Table).

Two-tailed analyses were performed, and significance was defined as a P value less than 0.05. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses.

Results

Incidence of COM

The incidence of pneumonia occurring before COM in the COM group was 9.3 % (n=2,168), whereas the incidence of pneumonia in the control group was 7.2% (n=6,754) during the follow-up period (p<0.001). The proportion of participants with a BMI over 23 in the COM group (63.9%) was significantly higher than that in the control group (p<0.001). The SBPs and DBPs of participants in the COM group were significantly lower than those of participants in the control group (p=0.003 in systolic and p=0.001 in diastolic). The number of participants with a CCI score greater than 1 point in the COM group was significantly higher than that in the control group (p<0.001), indicating that the number or severity of comorbid conditions was high in the COM group. The alcohol consumption frequency was significantly lower in the COM group than in the control group, but there was no difference in smoking status. In addition, there was no difference in fasting blood glucose level or total cholesterol level between the 2 groups (Table 1).

OR of Pneumonia for COM

The adjusted OR of pneumonia for COM was 1.31 (95% CI=1.25–1.38, p<0.001), which was significantly higher regardless of age, gender, income, and residence region. In addition, the ORs were higher in the less than 60 years and female group in the model adjusted for obesity, smoking status, alcohol consumption, SBP, DBP, fasting blood glucose level, total cholesterol level, and CCI score (Table 2).

OR of the Number of Participants Diagnosed with Pneumonia for Periods before the Index Date

We verified whether the greater number of pneumonia events was related to the likelihood of having COM. The adjusted OR for COM in the group diagnosed with pneumonia ≥5 times was 1.34 (95% CI=1.20–1.49, p<0.001) during the total period, and the incidence of COM was significantly higher in all ages and gender. The adjusted OR of the group with 5 or more pneumonia diagnoses during 1 year from the index date for COM was 1.60 (95% CI=1.27–2.02, p<0.001). In addition, the incidences of COM in all age groups and females were significantly higher than those in the group with fewer than 5 cases of pneumonia. The adjusted ORs of participants who had been diagnosed with pneumonia ≥5 times 2 and 3 years before being diagnosed with COM were 1.44 (95% CI=1.21–1.71, p<0.001) and 1.41 (95% CI=1.21–1.63, p<0.001), respectively, and subgroup analysis according to age and gender showed the same results as those in 1 year (Table 3).

The OR of the number of patients diagnosed with pneumonia (per 5 cases of pneumonias) for COM was 1.12 (95% CI=1.08–1.16, p<0.001, S1 Table). In addition, the ORs by period (1, 2, and 3 years) for COM were 1.41 (95% CI=1.26–1.57, p<0.001), 1.28 (95% CI=1.19–1.38, p<0.001), and 1.22 (95% CI=1.15–1.30, p<0.001), respectively.

Discussion

The likelihood of pneumonia events before COM was greater in the COM group than the control group. In addition, the ORs of pneumonia in the COM group were significantly higher than those in the control group in all subgroups by age and gender. The OR for COM in the group that received pneumonia treatment ≥ 5 times was considerably higher than that in the group that received pneumonia treatment < 5 times, and the highest OR was found in the group diagnosed with pneumonia ≥ 5 times during the first year before the index date. As the number of pneumonia diagnoses increased and the period from the date of pneumonia diagnosis to the index date was shorter, a higher OR for COM was found. Previ-

Table 1
General Characteristics of Participants.

Characteristics	Total participants		
	Chronic otitis media (n, %)	Control (n, %)	P-value
Age (years old)			1.000
40-44	107 (0.5)	428 (0.5)	
45-49	2,177 (9.3)	8,708 (9.3)	
50-54	4,216 (18.0)	16,864 (18.0)	
55-59	4,280 (18.3)	17,120 (18.3)	
60-64	3,811 (16.3)	15,244 (16.3)	
65-69	3,542 (15.1)	14,168 (15.1)	
70-74	2,784 (11.9)	11,136 (11.9)	
75-79	1,660 (7.1)	6,640 (7.1)	
80-84	698 (3.0)	2,792 (3.0)	
85+	161 (0.7)	644 (0.7)	
Sex			1.000
Male	11,233 (47.9)	44,932 (47.9)	
Female	12,203 (52.1)	48,812 (52.1)	
Income			1.000
1 (lowest, HA with HI 1-2)	3,952 (16.9)	15,808 (16.9)	
2 (HI 3-4)	3,165 (13.5)	12,660 (13.5)	
3 (HI 5-6)	3,733 (15.9)	14,932 (15.9)	
4 (HI 7-8)	4,862 (20.8)	19,448 (20.8)	
5 (highest, HI 9-10)	7,724 (33.0)	30,896 (33.0)	
Region of residence			1.000
Urban	10,275 (43.8)	41,100 (43.8)	
Rural	13,161 (56.2)	52,644 (56.2)	
Obesity †			<0.001*
Underweight	516 (2.2)	2,292 (2.4)	
Normal	7,931 (33.8)	33,394 (35.6)	
Overweight	6,619 (28.2)	25,448 (27.2)	
Obese I	7,618 (32.5)	29,765 (31.8)	
Obese II	752 (3.2)	2,845 (3.0)	
Smoking status			0.051
Nonsmoker	17,082 (72.9)	68,020 (72.6)	
Past smoker	2,807 (12.0)	10,966 (11.7)	
Current smoker	3,547 (15.1)	14,758 (15.7)	
Alcohol consumption			0.009*
< 1 time a week	16,319 (69.6)	64,446 (68.8)	
≥ 1 time a week	7,117 (30.4)	29,298 (31.3)	
Systolic blood pressure			0.003*
< 120 mmHg	7,160 (30.6)	28,018 (29.9)	
120-139 mmHg	11,508 (49.1)	45,739 (48.8)	
≥ 140 mmHg	4,768 (20.3)	19,987 (21.3)	
Diastolic blood pressure			0.001*
< 80 mmHg	11,103 (47.4)	43,538 (46.4)	
80-89 mmHg	8,591 (36.7)	34,370 (36.7)	0.941
≥ 90 mmHg	3,742 (16.0)	15,836 (16.9)	
Fasting blood glucose			
< 100 mg/dL	14,702 (62.7)	58,708 (62.6)	
100-125 mg/dL	6,544 (27.9)	26,283 (28.0)	
≥ 126 mg/dL	2,190 (9.3)	8,753 (9.3)	
Total cholesterol			0.216
< 200 mg/dL	12,474 (53.2)	49,513 (52.8)	
200-239 mg/dL	7,683 (32.8)	31,290 (33.4)	
≥ 240 mg/dL	3,279 (14.0)	12,941 (13.8)	
CCI score (score)			<0.001*
0	15,613 (66.6)	64,943 (69.3)	
1	3,683 (15.7)	12,967 (13.8)	
2	1,908 (8.1)	7,148 (7.6)	
3	977 (4.2)	3,655 (3.9)	
≥ 4	1,255 (5.4)	5,031 (5.4)	
Pneumonia			<0.001*
Yes	2,168 (9.3)	6,754 (7.2)	
No	21,268 (90.8)	86,990 (92.8)	

Abbreviations: CCI, Charlson comorbidity index; HA, health aid; HI, Health insurance
* Chi-square test. Significance at $P < 0.05$
† Obesity (BMI, body mass index, kg/m^2) was categorized as < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II).

ous studies on the relationship between respiratory tract diseases and otitis media have mainly been conducted on the URT of children (Doyle and Alper, 2003; Pettigrew et al., 2011; Pettigrew et al., 2012). The epidemiological and pathophysiological associations between LRT diseases, including pneumonia and COM, have not been published thus far, especially in adults.

One piece of pathophysiological evidence demonstrating an epidemiological association between pneumonia and COM may be microbiome dysbiosis. Pathogens invading into the lung parenchyma and LRT can induce alterations in microbiome dynamics leading to immune modulation, such as changes in circulating lymphocytes (Budden et al., 2017). LRT infection and inflammation may

Table 2
Crude and adjusted odd ratios (95% confidence interval) of pneumonia for chronic otitis media with stratified subgroup according to age and sex.

Characteristics	N of Chronic otitis media (exposure/total, %)	N of Control (exposure/total, %)	ORs for chronic otitis media			
			Crude†	P-value	Adjusted†,‡	P-value
Total participants (n = 117,180)						
Pneumonia	2,168/23,436 (9.3%)	6,754/93,744 (7.2%)	1.32 (1.26-1.39)	<0.001*	1.31 (1.25-1.38)	<0.001*
Non- Pneumonia	21,268/23436 (90.7%)	86,990/93,744 (92.8%)	1		1	
Age < 60 years old (n = 53,900)						
Pneumonia	620/10,780 (5.8%)	1,750/43,120 (4.1%)	1.44 (1.31-1.59)	<0.001*	1.43 (1.30-1.57)	<0.001*
Non- Pneumonia	101,60/10,780 (94.2%)	41,370/43,120 (95.9%)	1		1	
Age ≥ 60 years old (n = 63,280)						
Pneumonia	1,548/12,656 (12.2%)	5,004/50,624 (9.9%)	1.28 (1.20-1.36)	<0.001*	1.27 (1.20-1.35)	<0.001*
Non- Pneumonia	11,108/12,656 (87.8%)	45,620/50,624 (90.1%)	1		1	
Men (n = 56,165)						
Pneumonia	1,003/11,233 (8.9%)	3,230/44,932 (7.2%)	1.28 (1.18-1.38)	<0.001*	1.27 (1.18-1.37)	<0.001*
Non- Pneumonia	10,230/11,233 (91.1%)	41,702/44,932 (92.8%)	1		1	
Women (n = 61,015)						
Pneumonia	1,165/12,203 (9.5%)	3,524/48,812 (7.2%)	1.36 (1.27-1.46)	<0.001*	1.35 (1.26-1.45)	<0.001*
Non- Pneumonia	11,038/12,203 (90.5%)	45,288/48,812 (92.8%)	1		1	

* Conditional logistic regression model, Significance at $P < 0.05$
† Stratified model for age, sex, income, and region of residence.
‡ Adjusted model for obesity, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol and CCI scores.

contribute to alteration of the oral cavity microbiome through immunologic crosstalk with the URT. Morinaga et al. reported that the alpha diversity of the oral cavity was significantly increased in a murine pneumonia model induced by *K. pneumoniae* inoculation, which supported the possibility that LRT infection could affect the microbiome composition of URT (Morinaga et al., 2019). In addition, the decrease in mucociliary clearance of respiratory epithelial cells due to pneumonia could also be related to URT microbiome dysbiosis, including that in the eustachian tube and middle ear mucosa. In addition, 1 of the factors that can alter the microbiome diversity of the respiratory mucosa in pneumonia may be antibiotic treatment. Most antibiotics reduce the diversity of the human microbiome and the abundance of commensal bacteria (Becattini et al., 2016; Dubourg et al., 2014). Several studies have reported that alteration of the gut or fecal microbiome is prominent not only when a single antibiotic is used but also when a combination therapy is used such as gentamicin-ampicillin and ciprofloxacin-metronidazole (Ferrer et al., 2014; Heinsen et al., 2015; Koido et al., 2014). Thus, antibiotic treatment for pneumonia can affect the abundance and diversity of the gut microbiome, and dysbiosis of the colonic microbiome influencing disparate sites via the gut-respiratory tract axis through lymphatic and systemic circulation may impact secondary tissue and immune homeostasis of the airways (Schuijt et al., 2016; Trivedi and Barve, 2020). This phenomenon can serve as microbiological evidence that can be associated with the development of diseases such as COM and chronic rhinosinusitis after pneumonia.

Mucus plugging in the airway caused by pneumonia induces hypoxic conditions and leads to the expression of inflammatory markers in the eustachian tube and middle ear mucosa. It may lead to cell death, such as apoptosis and necrosis of airway epithelial/endothelial cells, and activate neutrophilic inflammation (Jiang et al., 2019; Mall et al., 2008). Interleukin (IL)-1 is a proinflammatory molecule that plays a crucial role in neutrophilic infiltration into the airway and tissue remodeling(Dinarello, 2018). IL-1 interacts with a domain of Toll-like receptors (TLRs) that mediate the recognition of pathogens, and the Toll-IL-1-receptor (TIR) domain mediates innate immune responses against pathogens and can also trigger a sepsis-associated cytokine storm (Cohen, 2014; Deng et al., 2013; Salomao et al., 2009). The mRNA and protein levels of TLR-2 and TLR-4 have been found to be markedly decreased in the middle ear mucosa of patients with chronic suppurative otitis media (CSOM) and cholesteatoma-associated COM (Hirai et al., 2013; Si et al., 2014). This effect is an important pathophysiological link between pneumonia and COM. The higher the frequency of expression of inflammatory signaling through the airway, the more likely it is to promote the accumulation of pathogens in the eustachian tube and middle ear mucosa. This link can be inferred from the results of this study showing that the OR of COM was high in the group with more than 5 pneumonia diagnoses.

Our study yielded an epidemiological association between pneumonia and COM using a nationwide population-based cohort database. The health check-up database based on age group for the national population in South Korea used in this study includes basic demographic information as well as objective values, such as blood pressure, fasting glucose, and total cholesterol levels. Therefore, this resource represents an advantage from which additional diverse health-related information can be used for analysis in addition to medical claim codes included in the database from the health insurance review and assessment service. In addition to simply analyzing the incidence of COM according to the presence or absence of pneumonia, we added the total number of pneumonia diagnoses before the index date and the number of pneumonia diagnoses during a specific period, such as 1, 2, and 3 years before the index date, as additional factors that can affect COM incidence to increase reliability.

Although this study postulates that pneumonia occurrence increases COM incidence, there are also a few limitations. First, since we retrospectively analyzed the data obtained from each cohort in this study, it is not possible to infer causality between pneumonia and COM. Second, additional information, such as microbiological culture results, including antibiotic susceptibility for pneumonia and COM, radiologic findings to determine the severity of pneumonia, the results of pulmonary function tests, and hearing thresholds, could not be obtained from the health screening cohort database. Expected confounding factors such as age, gender, income level, and residence area were matched 1:4 with the control group to improve the reliability of the results. However, we could not obtain specific data to support the functional decline of the respiratory epithelium from hypoxia and microbiome dysbiosis between the 2 diseases. In addition, 1 of the limitations was that variables such as frequency of upper respiratory infection and antibiotic usage, which could affect the incidence of pneumonia and COM, were not included in the analysis due to limitation of data availability. Finally, the number of medical encounters according to pneumonia diagnosis may be higher than that in the control group. Therefore, this discrepancy can affect the index date, which is the diagnosis date of COM as a possible confounder, and data curation

Table 3
Crude and adjusted odd ratios (95% confidence interval) of the number of diagnosed with pneumonia by period for chronic otitis media with stratified subgroup according to age and sex.

Characteristics	N of Chronic otitis media (exposure/total, %)	N of Control (exposure/total, %)	ORs for chronic otitis media			
			Crude[†]	P-value	Adjusted[†,‡]	P-value
Number of diagnosed with pneumonia before the index date						
Total participants (n = 117,180)						
Pneumonia ≥ 5	448/23,436 (1.9%)	1338/93,744 (1.4%)	1.35 (1.21-1.51)	<0.001*	1.34 (1.20-1.49)	<0.001*
Pneumonia < 5	22,988/23,436 (98.1%)	92406/93,744 (98.6%)	1		1	
Age < 60 years old (n = 53,900)						
Pneumonia ≥ 5	93/10,780 (0.9%)	252/43,120 (0.6%)	1.48 (1.17-1.88)	0.001*	1.47 (1.16-1.86)	0.002*
Pneumonia < 5	10,687/10,780 (99.1%)	42868/43,120 (99.4%)	1		1	
Age ≥ 60 years old (n = 63,280)						
Pneumonia ≥ 5	355/12,656 (2.8%)	1086/50,624 (2.1%)	1.32 (1.17-1.49)	<0.001*	1.31 (1.16-1.48)	<0.001*
Pneumonia < 5	12,301/12,656 (97.2%)	49538/50,624 (97.9%)	1		1	
Men (n = 56,165)						
Pneumonia ≥ 5	209/11,233 (1.9%)	697/44,932 (1.6%)	1.21 (1.03-1.41)	0.019*	1.19 (1.02-1.39)	0.030*
Pneumonia < 5	11,024/11,233 (98.1%)	44235/44,932 (98.4%)	1		1	
Women (n = 61,015)						
Pneumonia ≥ 5	239/12,203 (2.0%)	641/48,812 (1.3%)	1.51 (1.30-1.75)	<0.001*	1.49 (1.28-1.73)	<0.001*
Pneumonia < 5	11,964/12,203 (98.0%)	48171/48,812 (98.7%)	1		1	
Number of diagnosed with pneumonia for 1 year before the index date						
Total participants (n = 117,180)						
Pneumonia ≥ 5	102/23,436 (0.4%)	252/93,744 (0.3%)	1.62 (1.29-2.05)	<0.001*	1.60 (1.27-2.02)	<0.001*
Pneumonia < 5	23,334/23,436 (99.6%)	93492/93,744 (99.7%)	1		1	
Age < 60 years old (n = 53,900)						
Pneumonia ≥ 5	21/10,780 (0.2%)	46/43,120 (0.1%)	1.83 (1.09-3.06)	0.022*	1.81 (1.08-3.03)	0.025*
Pneumonia < 5	10,759/10,780 (99.8%)	43074/43,120 (99.9%)	1		1	
Age ≥ 60 years old (n = 63,280)						
Pneumonia ≥ 5	81/12,656 (0.6%)	206/50,624 (0.4%)	1.58 (1.22-2.04)	0.001*	1.56 (1.21-2.02)	0.001*
Pneumonia < 5	12,575/12,656 (99.4%)	50418/50,624 (99.6%)	1		1	
Men (n = 56,165)						
Pneumonia ≥ 5	49/11,233 (0.4%)	149/44,932 (0.3%)	1.32 (0.95-1.82)	0.095	1.30 (0.94-1.80)	0.113
Pneumonia < 5	11,184/11,233 (99.6%)	44783/44,932 (99.7%)	1		1	
Women (n = 61,015)						
Pneumonia ≥ 5	53/12,203 (0.4%)	103/48,812 (0.2%)	2.07 (1.48-2.88)	<0.001*	2.04 (1.46-2.85)	<0.001*
Pneumonia < 5	12,150/12,203 (99.6%)	48709/48,812 (99.8%)	1		1	
Number of diagnosed with pneumonia for 2 years before the index date						
Total participants (n = 117,180)						
Pneumonia ≥ 5	179/23,436 (0.8%)	496/93,744 (0.5%)	1.45 (1.22-1.72)	<0.001*	1.44 (1.21-1.71)	<0.001*
Pneumonia < 5	23,257/23,436 (99.2%)	93248/93,744 (99.5%)	1		1	
Age < 60 years old (n = 53,900)						
Pneumonia ≥ 5	43/10,780 (0.4%)	103/43,120 (0.2%)	1.67 (1.17-2.39)	0.005*	1.66 (1.16-2.37)	0.006*
Pneumonia < 5	10,737/10,780 (99.6%)	43017/43,120 (99.8%)	1		1	
Age ≥ 60 years old (n = 63,280)						
Pneumonia ≥ 5	136/12,656 (1.1%)	393/50,624 (0.8%)	1.39 (1.14-1.69)	0.001*	1.38 (1.13-1.68)	0.001*
Pneumonia < 5	12,520/12,656 (98.9%)	50231/50,624 (99.2%)	1		1	
Men (n = 56,165)						
Pneumonia ≥ 5	84/11,233 (0.7%)	277/44,932 (0.6%)	1.22 (0.95-1.55)	0.119	1.21 (0.94-1.54)	0.138
Pneumonia < 5	11,149/11,233 (99.3%)	44655/44,932 (99.4%)	1		1	
Women (n = 61,015)						
Pneumonia ≥ 5	95/12,203 (0.8%)	219/48,812 (0.4%)	1.74 (1.37-2.22)	<0.001*	1.73 (1.36-2.20)	<0.001*
Pneumonia < 5	12,108/12,203 (99.2%)	48593/48,812 (99.6%)	1		1	
Number of diagnosed with pneumonia for 3 years before the index date						
Total participants (n = 117,180)						
Pneumonia ≥ 5	239/23,436 (1.0%)	677/93,744 (0.7%)	1.42 (1.22-1.65)	<0.001*	1.41 (1.21-1.63)	<0.001*
Pneumonia < 5	23,197/23,436 (99.0%)	93067/93,744 (99.3%)	1		1	
Age < 60 years old (n = 53,900)						
Pneumonia ≥ 5	54/10,780 (0.5%)	137/43,120 (0.3%)	1.58 (1.15-2.17)	0.005*	1.56 (1.14-2.15)	0.006*
Pneumonia < 5	10,726/10,780 (99.5%)	42983/43,120 (99.7%)	1		1	
Age ≥ 60 years old (n = 63,280)						
Pneumonia ≥ 5	185/12,656 (1.5%)	540/50,624 (1.1%)	1.38 (1.16-1.63)	<0.001*	1.37 (1.16-1.62)	<0.001*
Pneumonia < 5	12,471/12,656 (98.5%)	50084/50,624 (98.9%)	1		1	
Men (n = 56,165)						
Pneumonia ≥ 5	117/11,233 (1.0%)	375/44,932 (0.8%)	1.25 (1.02-1.54)	0.035*	1.24 (1.00-1.53)	0.046*
Pneumonia < 5	11,116/11,233 (99.0%)	44557/44,932 (99.2%)	1		1	
Women (n = 61,015)						
Pneumonia ≥ 5	122/12,203 (1.0%)	302/48,812 (0.6%)	1.62 (1.31-2.01)	<0.001*	1.61 (1.30-1.99)	<0.001*
Pneumonia < 5	12,081/12,203 (99.0%)	48510/48,812 (99.4%)	1		1	

* Conditional logistic regression model, Significance at $P < 0.05$
† Stratified model for age, sex, income, and region of residence.
‡ Adjusted model for obesity, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol and CCI scores.

for the number of medical encounters is needed to minimize this potential effect in future research.

Conclusion

This research demonstrated that pneumonia diagnosis was significantly associated with an increased COM incidence. In addition, ≥5 pneumonia diagnoses significantly increased COM incidence. Therefore, the results of the present study suggest a new perspective that infection of the LRT may affect the function of the eustachian tube and the middle ear to later cause COM.

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Author Contributions

S.K.K., H.G.C., and C.M. handled the conceptualization and design for this study. D.M.Y. and C.M. analyzed and interpreted the data. H.G.C., S.J.H., I.P., and C.M. were responsible for curating the data. Writing, original draft preparation—S.K.K. and H.G.C. wrote the manuscript and reviewed important intellectual content. All authors have read and agreed to the published version of the manuscript.

Ethic statement

The ethics committee of Hallym University (2019-10-023) permitted this study. Written informed consent was waived by the institutional review board owing to the retrospective nature of this study. All analyses adhered to the guidelines and regulations of the ethics committee of Hallym University.

Data sharing

All the data are available from the database of the NHISS (https://nhiss.nhis.or.kr/). NHISS allows access to the data by any researcher who pledges to follow the research ethics guidelines and pay a fee.

Declaration of Competing Interest

The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.02.040.

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