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Inhaled corticosteroid increased the risk of adrenal insufficiency in patients with chronic airway diseases: a nationwide population-based study

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Inhaled corticosteroids (ICS) are commonly used for airway disease, but concerns about adrenal insufficiency (AI) have arisen. This retrospective observational study investigated the link between ICS use and AI risk using data from the National Health Insurance Service-National Sample Cohort, analyzing 66,631 patients with COPD (Korean Standard Classification of Diseases [KCD] codes J42-J44) or asthma (KCD codes J45-J46). ICS use, daily dosage, and AI cases (hospitalization or ≥ 2 outpatient visits with KCD code E27) were identified via diagnostic codes. Cox proportional hazard survival analysis and inverse probability of treatment weighting (IPTW) addressed baseline differences between ICS and non-ICS users. In total 66,631 patients, the mean age was 57.3 years, 42.6% were male, and 42.2% had a Charlson comorbidity index (CCI) of 2 or higher. Among the patients, 15.5% used ICS, with a mean daily dose of 404.2 µg/day. The incidence of AI was higher in ICS users (1.69 per 1000) than in non-users (0.54 per 1000). ICS use independently increased AI risk (HR: 3.06, 95% CI: 1.82–5.14, $p < 0.001$). Each 100 µg/day increase in ICS was associated with a 3% increase in AI incidence (HR: 1.03, 95% CI: 1.02–1.04, $p < 0.001$). Quartile analysis indicated a significant AI risk increase across all ICS dosage quartiles compared with non-users. Subgroup analysis showed consistent associations with age, sex, and smoking, with stronger links in systemic steroid users (HR: 3.54, 95% CI: 2.10–5.96, $p < 0.001$) and those with higher CCI (HR: 2.61, 95% CI: 1.64–4.12, $p < 0.001$). ICS may use increases AI risk in chronic airway disease patients, particularly among systemic steroid users and those with higher CCI. Close monitoring of high-risk patients is advised, and further research is needed to clarify mechanisms and optimize safe ICS use.

Keywords Glucocorticoids, Chronic Airway diseases, Respiratory Tract diseases, Adrenal dysfunction, Inhaled Corticosteroid Safety, Inverse probability treatment weighting, Retrospective cohort study

Abbreviations

COPD	Chronic Obstructive Airway Diseases
AI	Adrenal Insufficiency
HPA	Hypothalamic-Pituitary-Adrenal
ICS	Inhaled Corticosteroids
NHIS	National Health Insurance Service
NSC	National Sample Cohort
NHID	National Health Insurance Database
KCD	Korean Standard Classification of Diseases
LAMA	Long-Acting Muscarinic Antagonists
LABA	Long-Acting Beta-Agonists

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SABA	Short-Acting Beta-Agonists
LTRA	Leukotriene Receptor Antagonists
CCI	Charlson Comorbidity Index
IPTW	Inverse Probability of Treatment Weighting
SMD	Standardised Mean Difference
KM	Kaplan-Meier
OR	Odds Ratio
CI	Confidence Interval
IQR	Interquartile Range
RCT	randomized controlled trial

Background

Chronic airway diseases, such as asthma and chronic obstructive pulmonary diseases (COPDs), comprise a heterogeneous group of conditions that predominantly affect the airways and alveoli and lead to persistent respiratory symptoms[1]. COPD prevalence in those aged 40 and older ranges from 7.38 to 12.64%[2]. The global burden of COPD is rising, particularly in low-income countries, due to factors such as aging populations, pollution, and smoking[3]. By 2050, the number of COPD cases is expected to increase by 23%, reaching approximately 600 million globally[4]. On the other hand, asthma prevalence dropped by 24%, mortality by 51%, and disability-adjusted life years by 43% from 1990 to 2019. However, global cases rose to 262 million, with low-income countries like Kiribati and Papua New Guinea showing low prevalence but high mortality[5]. These statistics emphasise the substantial social, health, and economic impacts of chronic obstructive airway diseases, necessitating effective management and prevention strategies.

Inhaled corticosteroids (ICS) effectively manage chronic airway diseases by reducing airway inflammation, enhancing treatment outcomes[6], and minimising systemic steroid side effects[7,8]. However, concerns have emerged regarding the potential of ICS to induce complications similar to those observed with systemic steroid use, including osteoporosis, skin thinning, and even adrenal insufficiency (AI)[8–10]. Long-term high-dose ICS use has raised concerns about hypothalamic-pituitary-adrenal (HPA) axis suppression, potentially leading to adrenal insufficiency (AI), similar to systemic steroids[11–15]. Previous studies had limitations, including insufficient analysis of dose dependency, case-control design, and small sample sizes ($n = 33$–392), leading to conflicting findings on AI risk associated with ICS use[16–20]. Moreover, there has been a lack of studies that broadly examine both asthma and COPD, despite ICS being widely used in managing both conditions, limiting the applicability of previous findings to these broader populations. While ICS is essential for managing airway diseases, its long-term safety has been assumed without sufficient studies or regulatory oversight, underscoring the need for a proper risk-benefit analysis. Therefore, this study aimed to investigate the relationship between ICS use and AI risk in individuals with chronic airway diseases such as COPD and asthma using nationwide claims data, providing a comprehensive, long-term evaluation across a large-scale population.

Methods

Data source

As of 2022, South Korea's National Health Insurance Service (NHIS) system covered 97.1% of the population, totalling 52,932,000 people. As a single insurer, the NHIS collects comprehensive medical information from all citizens and constructs the National Health Insurance Database (NHID)[21]. We used the NHIS National Sample Cohort (NSC), (version 2.2), a 1-million-person sample (2.2% of the total population) from the NHID in 2006. The NHIS-NSC participants were selected using a systematic stratified random sampling based on 2,142 strata defined by sex, age, income level (insurance type and insurance premium), and residential region, ensuring it is representative of the South Korean population (https://nhiss.nhis.or.kr). Information on cohort participants from the 2006 NHID was collected retrospectively (2002–2005) and prospectively (2007–2019), with annual additions of newborns and exclusions of deceased or emigrated individuals. It contained comprehensive information on insurance eligibility, medical history, healthcare providers, and health examination records. The NHIS ensures privacy through a three-step de-identification process: all personal identifiers are anonymized, sensitive diseases and procedures such as AIDS are generalized, and rare conditions are masked. Moreover, researchers can access the dataset only through the remote server access, and export only processed results such as tables and figures to prevent data leakage. Despite these measures, ethical concerns remain regarding privacy breaches and potential re-identification risks when using large-scale, de-identified health data; therefore, the NHIS rigorously restrict the use of the dataset for commercial or non-ethical purposes through a strict ethical review process.

Ethical considerations

The study protocol was approved by the Institutional Review Board of the Soonchunhyang University Seoul Hospital (2023-06-008), and the requirement for informed consent was waived due to the de-identified nature of the NHIS-NSC dataset.

Study population

Our study included patients who met the following criteria between 2002 and 2019: (1) two or more medical institute visits with a primary or secondary diagnosis of COPD (Korean Standard Classification of Diseases [KCD] codes J42-J44) (excluding J430 [pulmonary emphysema]) or asthma (KCD codes J45-J46) within one year of the first diagnosis date, and (2) at least two instances of respiratory medication use within one year after diagnosis, starting from the first prescription date. The sole diagnosis of emphysema (KCD J4830) was excluded

as it does not allow for the determination of the presence of airway obstruction. Respiratory medications included ICS, long-acting muscarinic antagonists (LAMA), ICS/long-acting beta-agonists (LABA), short-acting beta-agonists, xanthine, leukotriene receptor antagonists (LTRA), and systemic steroids. We initially screened 238,298 eligible patients (Fig. 1). We then applied several exclusion criteria, which included individuals diagnosed with COPD or asthma in during the 2002–2003 washout period to avoid counting pre-existing AI cases (as NHIS data only begins in 2002). Patients with less than one year of follow-up in 2019 ($n=44,324$) were also excluded due to insufficient follow-up duration. Additional, we excluded participants with claims of an AI diagnosis code before the index date ($n=189$), those under 18 years of age ($n=86,099$), and those lacking a national health examination before or at the index date for baseline covariates or missing major covariates ($n=38,625$ and $n=2,430$, respectively). The final study included a cohort of 66,631 patients.

Exposure assessment

The exposure status was determined based on treatment claims within the NHIS system. Participants were categorised as either "ICS users" or "non-ICS users" based on the presence or absence of ICS medication records during the follow-up period. For the dose-dependent associations, we calculated the mean daily dose, which referred to the total quantity of medication administered during the follow-up period divided by the prescription duration. The doses were converted to fluticasone equivalents to account for the varying potencies of the ICS medications. The equivalence ratios were fluticasone (50 mg), budesonide (80 mg), ciclesonide (32 mg), and beclomethasone (100 mg)[22–25].

Outcome assessment

Our primary outcome was the occurrence of AI coded under the KCD code E27 (Table S1). We defined this outcome as hospitalisation or two or more outpatient visits with the KCD code E27 as the primary or secondary diagnosis after the index date.

The index date referred to the date when a patient begins to be observed for study outcomes. For ICS users, the index date was the first ICS prescription date, whereas for non-ICS users, it was the date of the diagnosis of chronic airway disease (asthma or COPD) (Fig. 2). To avoid misclassification bias, participants with AI events occurring between the diagnosis of chronic airway disease and the first ICS prescription in ICS users were assigned to the non-ICS group. We also collected and adjusted for information on covariates, including demographics, socioeconomic status (incomes or insurance status) at the index date, smoking status before the index date, comorbidities (dyslipidaemia, hypertension, arrhythmia, infection, non-tuberculous mycobacterial infection, fungal infection, invasive pulmonary aspergillosis, and Charlson Comorbidity Index [CCI]) during the year before the index date, and simultaneous use of other drugs (LABA, LABA/LAMA, LAMA, SABA, xanthine, LTRA, and systemic steroids). Follow-up (survival time) started from the index date and lasted until AI occurrence, death, or the end of the study period (31 December 2019), whichever occurred first.

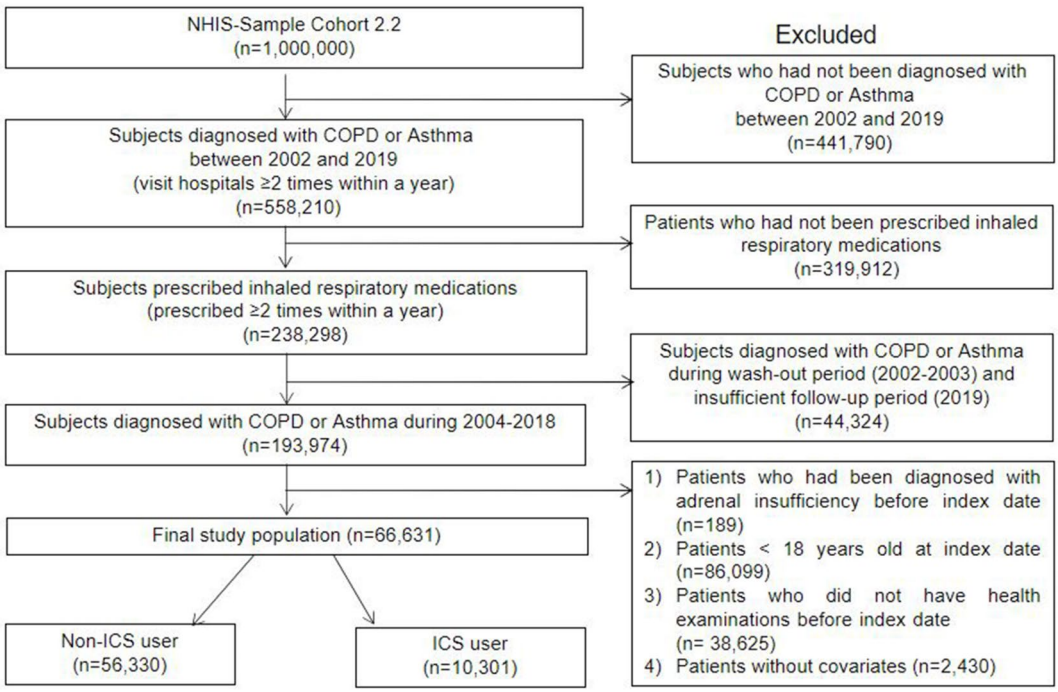

Fig. 1. Enrollment of patients. COPD = chronic obstructive pulmonary disease; NHIS = National Health Insurance Service; ICS = inhaled corticosteroids.

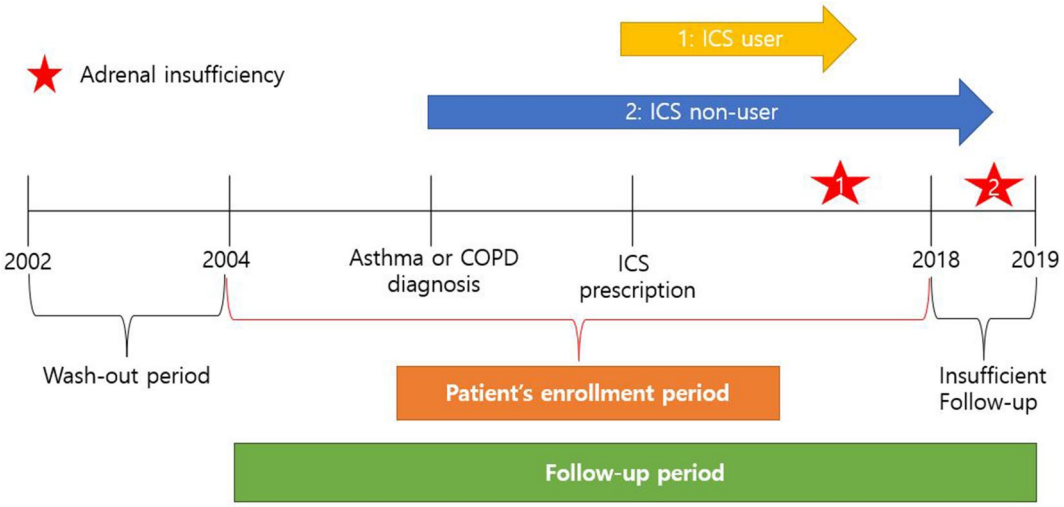

Fig. 2. Timeline of study design. COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids.

Statistical analysis

We compared the baseline characteristics between ICS and non-ICS users using the t-test for mean differences and the chi-squared test for frequency differences. To address any baseline characteristic imbalances between ICS and non-ICS users, we utilised the inverse probability of treatment weighting (IPTW) based on the propensity score method[26] (Fig. S1.). We selected IPTW because it retains the full sample size, unlike propensity score matching, ensuring better statistical power and a more representative population while effectively balancing covariates to minimize selection bias[27]. Pre-selected covariates, both prognostically significant and influencing treatment selection[28], were regressed to calculate the probability of receiving treatment. Upon applying IPTW, we considered the covariates to be balanced between ICS and non-ICS users when the standardised mean difference (SMD) was < 0.10, based on previous studies[29–31]. Detailed statistical methods were described in Fig. S2.

The incidence rate was expressed as the number of incident cases per 1,000 person-years (AI cases / total person-years × 1,000). The Cox PH proportional hazards model was used to assess the association between ICS use and AI risk, estimating both unadjusted (pre-IPTW) and adjusted (post-IPTW) hazard ratios (HRs) with 95% confidence intervals (CIs). The PH assumption was satisfied ($p = 0.185$).To account for multiple comparisons and reduce the risk of false positives, we applied the Bonferroni-Holm correction, which adjusts the significance level based on the number of tests performed, across all analyses. Kaplan-Meier (KM) survival curves were generated to illustrate the cumulative AI incidence over time, and the groups were compared using the log-rank test. To address the potential bias introduced by early diagnosis, we performed landmark analyses at specific time points (6 months, 1 year, and 2 years) to assess the effect of the ICS on AI beyond these time points. Continuous users are defined as those who received at least one additional ICS prescription within 30 days of a visit, while intermittent users are defined as those who did not meet this criterion. For the dose-dependent analysis, we divided the daily ICS dose into continuous and categorical variables for analysis based on the average daily ICS dose from the index to the last follow-up. In the continuous analysis, we calculated the HR per increase of 100 μg/day of fluticasone. We categorised the daily dose, equivalent to fluticasone dose into three groups: high (1000 ug/day), medium (500–999 ug/day), and low (less than 500 ug/day) based on the previous study[32]. Quartiles (Q) for ICS use were expressed as equivalent fluticasone doses: Q1 (median = 100.0 μg/day), Q2 (185.7 μg/day), Q3 (300.0 μg/day), and Q4 (541.7 μg/day). Participants in our study were categorized based on receiving any specific ICS ingredient at least once, and these groups were then compared with ICS non-users to analyse HRs. We conducted subgroup analyses to identify groups of ICS users more susceptible to AI risk based on factors such as gender, age (under 65 vs. 65 and older), smoking status (never vs. ever), income (low [0 to 3rd], middle [4th to 7th], high [8th to 10th]), underlying airway disease classification (asthma, COPD, and both [diagnosed with both within one year]), systemic steroid use and dosage (low-dose [cumulative prednisolone dose < 250 mg], high-dose [cumulative prednisolone dose ≥ 250 mg])[33], and CCI score (< 2 score vs. ≥ 2 score)[34]. We performed subgroup analysis on the pre-IPTW cohort using conventional Cox regression with the same variables employed in the IPTW analysis to calculate adjusted HRs. Each subgroup analysis was conducted after stratification, excluding the stratification variable from the subgroup model. Large database processing and descriptive statistics were performed using SAS Enterprise Guide version 8.3 (SAS Institute Inc., Cary, NC, USA) and IPTW method and Cox PH analysis were performed using *WeightIt* and *survival* packages in R Studio version 4.3.0 (RStudio Inc., Boston, MA, USA).

Characteristic	ICS users	Non-ICS users	*p*-value*	SMD before IPTW	SMD after IPTW
Number of patients	10,301 (15.5)	56,330 (84.5)			
Age	62.0 ± 15.1	56.4 ± 14.9	< 0.001	-0.370	-0.047
Male	4,667 (45.3)	23,729 (42.1)	< 0.001	0.032	0.014
Smoking status					
Never	6,540 (63.5)	39,859 (70.8)	< 0.001	0.073	0.006
Former	1,466 (14.2)	5,490 (9.8)		-0.045	-0.002
Current	2,295 (22.3)	10,981 (19.5)		-0.028	-0.004
BMI	24.1 ± 3.7	23.9 ± 13.6	0.003	-0.020	-0.011
Year of diagnosis					
2002–2007	3,552 (34.5)	9,840 (17.5)	< 0.001	-0.170	0.027
2008–2011	1,516 (14.7)	16,436 (29.2)		0.145	0.022
2012–2014	1,241 (12.1)	14,738 (26.2)		0.141	-0.003
2015–2018	3,992 (38.8)	15,316 (27.2)		-0.116	-0.047
Income					
Medical aid	543 (5.3)	365 (0.7)	< 0.001	-0.046	0.001
Low (1st to 3rd)	2,205 (21.4)	12,353 (21.9)		0.005	0.001
Middle (4th to 7th)	3,358 (32.6)	20,590 (36.6)		0.040	0.000
High (8th to 10th)	4,195 (40.7)	23,022 (40.9)		0.002	-0.002
Comorbidity					
COPD	656 (6.4)	6,893 (12.2)	< 0.001	0.059	-0.007
Asthma	6,833 (66.3)	41,299 (73.3)		0.070	0.006
Both COPD and asthma	2,812 (27.3)	8,138 (14.5)		-0.129	0.001
Diabetes mellitus	1,670 (16.2)	6,915 (12.3)	< 0.001	NC	NC
Dyslipidaemia	2,486 (24.1)	8,874 (15.8)	< 0.001	-0.084	-0.007
Hypertension	3,758 (36.5)	16,456 (29.2)	< 0.001	-0.073	0.000
Ischemic heart disease	993 (9.6)	3,400 (6.0)	< 0.001	NC	NC
Arrhythmia	423 (4.1)	1,190 (2.1)	< 0.001	-0.020	-0.001
Infection	39 (0.38)	43 (0.08)	< 0.001	-0.003	0.000
NTM	22 (0.21)	19 (0.03)	< 0.001	-0.002	0.000
Fungal infection	10 (0.10)	10 (0.02)	< 0.001	-0.001	0.000
IPA	10 (0.10)	8 (0.01)	< 0.001	-0.001	0.000
Renal failure	159 (1.54)	303 (0.54)	< 0.001	NC	NC
Malignancy	653 (6.34)	2,273 (4.04)	< 0.001	NC	NC
CCI score ≥ 2	4,799 (46.6)	23,306 (41.4)	< 0.001	-0.052	-0.002
Medication					
ICS only	4,493 (43.6)	NA			
ICS/LABA	8,145 (79.1)	NA			
LABA only	2,732 (26.5)	23,955 (42.5)	< 0.001	0.160	-0.007
LABA/LAMA	254 (2.5)	252 (0.5)	< 0.001	-0.020	0.000
LAMA only	2,271 (22.1)	2,019 (3.6)	< 0.001	-0.185	-0.002
SABA	5,922 (57.5)	20,680 (36.7)	< 0.001	-0.208	-0.032
Xanthine	5,445 (52.9)	32,726 (58.1)	< 0.001	0.052	-0.004
LTRA	7,484 (72.7)	34,723 (61.6)	< 0.001	-0.110	-0.011
Systemic steroid	3,863 (37.5)	27,620 (49.0)	< 0.001	0.115	0.017

Table 1. Baseline demographics before and after IPTW. Data are presented as mean ± standard deviation, or number (%). *p-value was calculated by t-test for mean difference and chi-squared test for frequency difference. SMD, standardised mean difference; IPTW = Inverse probability of treatment weighting; COPD = Chronic obstructive pulmonary disease; NTM = Non-tuberculous mycobacteria; IPA = Invasive pulmonary aspergillosis; CCI, Charlson comorbidity index; ICS = Inhaled corticosteroids; BMI = Body mass index; NC, not calculated; NA, not applicable; LABA = Long-acting beta-agonist; LAMA = Long-acting muscarinic antagonist; SABA, short-acting beta-agonist; LTRA = Leukotriene receptor antagonist.

Results

Demographic findings

Among the 66,631 patients, the mean age was 57.3 years, 42.6% were male, and 69.6% had never smoked. Of these, 11.3% had COPD, 72.2% had asthma, 16.4% had both diagnoses, and 42.2% had a CCI of 2 or higher.

A total of 10,301 (15.5%) patients were ICS users, and 56,330 (84.5%) were non-ICS users (Table 1). ICS users were older, had more medical conditions, including both COPD and asthma diagnoses simultaneously, and received more LAMA, SABA, and LTRA prescriptions, but less LABA and systemic steroids. Differences were observed in the years since diagnosis. Among ICS users, the mean daily dose was 404.2 ± 522.1 μg/day, and the cumulative dose was 7859.0 ± 53032.9 μg. The ICS prescription details for ICS were described in the Table S2. During a follow-up period (median = 6.08 years [IQR: 3.15–9.73]), 980 (9.5%) deaths occurred among ICS users and 6,392 (11.4%) among non-ICS users. The median follow-up time from index to censoring was 2.72 years (IQR 1.45) for ICS users and 7.14 years (IQR 6.21) for non-ICS users. After IPTW matching, all covariates were balanced (SMD < 0.1) (Fig. S1).

AI incidence and ICS use

AI occurred in 272 cases. ICS users had a higher incidence of AI compared to non-ICS users ($p < 0.001$) (Table 2). When daily doses were categorised into three groups, medium-dose ICS users had the highest AI incidence rate (1.90 per 1,000 person-years), followed by low-dose (1.69 per 1,000 person-years, $p < 0.001$), but not high-dose users (1.16 per 1,000 person-years, $p = 0.273$). In the quartile analysis of daily doses, AI incidence consistently increased significantly in each quartile compared to that in non-ICS users. Both intermittent and continuous ICS use resulted in higher AI rates than in non-ICS users. All ICS ingredients significantly increased AI occurrence, with ciclosonide demonstrating the highest incidence.

ICS dose and AI risk

In the unadjusted Cox proportional hazard (PH) analysis conducted before IPTW, the use of ICS was associated with an increased risk of AI (unadjusted hazard ratio [HR]: 3.22, 95% CI: 2.26–4.60) (Table 3; Fig. 3A). In the weighted Cox PH analysis after IPTW matching, ICS use independently increased the risk of AI occurrence (HR: 3.06, 95% CI: 1.82–5.14) (Table 3; Fig. 3B). These findings remained consistent in landmark analyses at 6 months (HR: 3.26, 95% CI: 1.86–5.79), 1 year (HR: 3.78, 95% CI: 2.01–7.11), and 2 years (HR: 3.55, 95% CI: 1.37–9.19) (Table 3).

In the continuous analysis of daily ICS dose, every increase of 100 μg/day in ICS was associated with a 3% increase in the incidence of AI (HR: 1.03, 95% CI: 1.02–1.04). In the categorical analysis divided into three categories, medium-dose ICS had the highest AI risk (HR: 3.38, 95% CI: 1.91–7.58), followed by low-dose ICS (HR: 3.00, 95% CI: 1.60–5.65), while high-dose ICS use showed no significant AI risk compared to non-ICS use (HR: 2.44, 95% CI: 0.46–13.03). In the quartile analysis of the daily ICS dose before IPTW, all quartiles (Q1-Q4) showed a significant increase in the incidence of AI compared to non-ICS users. However, after IPTW, there was a significant increase in the incidence in Q2-Q4, excluding Q1. Q2 exhibited the highest HR (HR, 5.38; 95% CI: 1.88–15.37). Both intermittent and continuous ICS use showed a significantly higher risk of AI incidence than in non-ICS use, both before and after IPTW. In the analysis based on ICS ingredients, all components

	Number	Total person-years	AI cases	Incidence rate (95% CI)†	*p*-value*
Non-ICS user	56,330	417,828	227	0.54 (0.47–0.62)	*reference*
ICS user	10,301	26,577	45	1.69 (1.24–2.27)	*< 0.001*
Daily dose analysis					
Three groups					
1000 ug/day	751	1,722	2	1.16 (0.14–4.20)	*0.273*
500–999 ug/day	2,400	5,780	11	1.90 (0.95–3.41)	*< 0.001*
< 500 ug/day	7,150	18,977	32	1.69 (1.15–2.38)	*< 0.001*
Quartiles					
Q1	2,121	5,484	10	1.82 (0.87–3.35)	*< 0.001*
Q2	2,191	5,726	9	1.57 (0.72–2.98)	*0.001*
Q3	2,838	7,766	13	1.67 (0.89–2.86)	*< 0.001*
Q4	3,151	7,601	13	1.71 (0.91–2.93)	*< 0.001*
Duration					
Intermittent use	5,063	12,574	19	1.51 (0.91–2.36)	*< 0.001*
Continuous use	5,238	14,003	26	1.86 (1.21–2.72)	*< 0.001*
ICS ingredient					
Fluticasone	5,770	15,713	25	1.59 (1.03–2.35)	*< 0.001*
Beclomethasone	1,371	3,607	6	1.66 (0.61–3.62)	*0.004*
Budesonide	5,818	14,730	20	1.36 (0.83–2.10)	*< 0.001*
Ciclesonide	441	1,232	3	2.44 (0.50–7.12)	*0.005*

Table 2. Incidence rate of adrenal insufficiency. † Incidence rate was calculated as follows: AI cases / total person-years per 1,000 people. *The p-value for the rate difference was calculated using non-ICS users as the reference group. ICS = inhaled corticosteroids; IPTW = inverse probability of treatment weighting; HR = hazard ratio; CI = confidence interval.

	Unadjusted (Pre-IPTW) HR (95% CI)	*P*-value	Adjusted HR (Post-IPTW) (95% CI)	*P*-value
ICS uses	**3.22 (2.26 to 4.60)**	**< 0.001***	**3.06 (1.82 to 5.14)**	**< 0.001***
Landmark analysis				
6 months	**3.26 (2.19 to 4.83)**	**< 0.001***	**3.26 (1.84 to 5.79)**	**< 0.001***
1 year	**3.41 (2.18 to 5.32)**	**< 0.001***	**3.78 (2.01 to 7.11)**	**< 0.001***
2 years	**3.92 (2.07 to 7.42)**	**< 0.001***	**3.55 (1.37 to 9.19)**	**0.009**
Daily dose analysis				
Continuous analysis per 100 ug/day	**1.02 (1.01 to 1.04)**	**0.009***	**1.03 (1.02 to 1.04)**	**< 0.001***
Three groups				
Non-ICS	reference		reference	
1000 ug/day	2.20 (0.54 to 8.94)	0.215	2.44 (0.60 to 9.99)	0.216
500–999 ug/day	**3.55 (1.90 to 6.63)**	**0.003***	**3.38 (1.51 to 7.58)**	**0.003***
< 500 ug/day	**3.22 (2.15 to 4.81)**	**< 0.001***	**3.00 (1.60 to 5.65)**	**< 0.001***
Quartiles				
Non-ICS	reference		reference	
Q1	**3.48 (1.81 to 6.69)**	**< 0.001***	1.50 (0.73 to 3.08)	0.264
Q2	**3.00 (1.51 to 5.94)**	**0.002***	**5.38 (1.88 to 15.37)**	**0.002***
Q3	**3.19 (1.79 to 5.70)**	**< 0.001***	**2.46 (1.16 to 5.24)**	**0.019**
Q4	**3.24 (1.81 to 5.80)**	**< 0.001***	**3.23 (1.55 to 6.76)**	**0.002***
Duration				
Non-ICS	reference		reference	
Intermittent use	**2.86 (1.75 to 4.69)**	**< 0.001***	**2.24 (1.22 to 4.12)**	**0.009**
Continuous use	**3.55 (2.30 to 5.48)**	**< 0.001***	**3.99 (1.95 to 8.19)**	**< 0.001***
ICS ingredient				
Non-ICS	reference		reference	
Fluticasone	**3.03 (1.95 to 4.70)**	**< 0.001***	**2.29 (1.10 to 4.77)**	**0.028**
Beclomethasone	**3.15 (1.38 to 7.20)**	**0.007***	4.37 (0.92 to 20.76)	0.063
Budesonide	**2.61 (1.61 to 4.23)**	**< 0.001***	**2.77 (1.33 to 5.77)**	**0.007**
Ciclesonide	**4.61 (1.46 to 14.55)**	**0.009***	**12.17 (3.79 to 39.15)**	**< 0.001***

Table 3. Cox proportional analysis for the risk of adrenal insufficiency according to ICS use. *Statistically significant at 0.05 level after Bonferroni-Holm correction to control probability of false rejections. ICS = inhaled corticosteroids; IPTW = inverse probability of treatment weighting; HR = hazard ratio; CI = confidence interval. Significant values are in bold.

showed a significantly higher incidence compared those in the non-ICS group in the unadjusted HR. However, in the adjusted HR, beclomethasone demonstrated marginal significance (HR: 4.37, 95% CI: 0.92–20.76), while ciclesonide continued to exhibit the highest HR (12.17, 95% CI: 3.79–39.15) for AI risk even after IPTW.

Analysis with multiple corrections also showed results similar to the main findings, indicating a risk associated with the use of ICS in the occurrence of AI. Particularly, continuous use and the use of ciclesonide were linked to this association.

Subgroup analysis

ICS use significantly increased AI risk in both age groups, including 65 years and older (HR: 3.98, 95% CI: 2.00–7.92) and under 65 years (HR: 2.08, 95% CI: 1.27–3.43) and both sex with males (HR: 4.54, 95% CI: 2.42–8.51) and females (HR: 1.74, 95% CI: 1.01–2.99) (Fig. 4). ICS use also raised AI risk in both never-smokers (HR: 2.46, 95% CI: 1.52–3.97) and ever-smokers (HR: 2.76, 95% CI: 1.31–5.81). In the subgroup analysis based on income categories, AI risk significantly increased in ICS users in the mid-income group (HR: 2.71, 95% CI: 1.23–5.97), and the high-income group (HR: 2.74, 95% CI: 1.48–5.08), with marginal significance in the low-income group. Classification based on the underlying airway disease showed an increased AI risk in patients with asthma (HR: 3.10, 95% CI: 1.84–5.23) and a marginally significant risk in patients with COPD (HR: 3.23, 95% CI: 0.86–12.16, $P = 0.082$).

In patients with systemic steroid use, ICS use significantly increased the risk of AI (HR: 3.54, 95% CI: 2.10–5.96), particularly in those with high systemic steroid use (HR: 3.22, 95% CI: 1.93–5.38). However, this risk was not significant in patients without systemic steroid use or with low systemic steroid use. Additionally, ICS use was associated with a higher AI risk in patients with a CCI score of ≥ 2 (HR: 2.61, 95% CI: 1.64–4.12), while the risk was marginal for those with a CCI score < 2 (HR: 2.11, 95% CI: 0.93–4.78, $P = 0.074$).

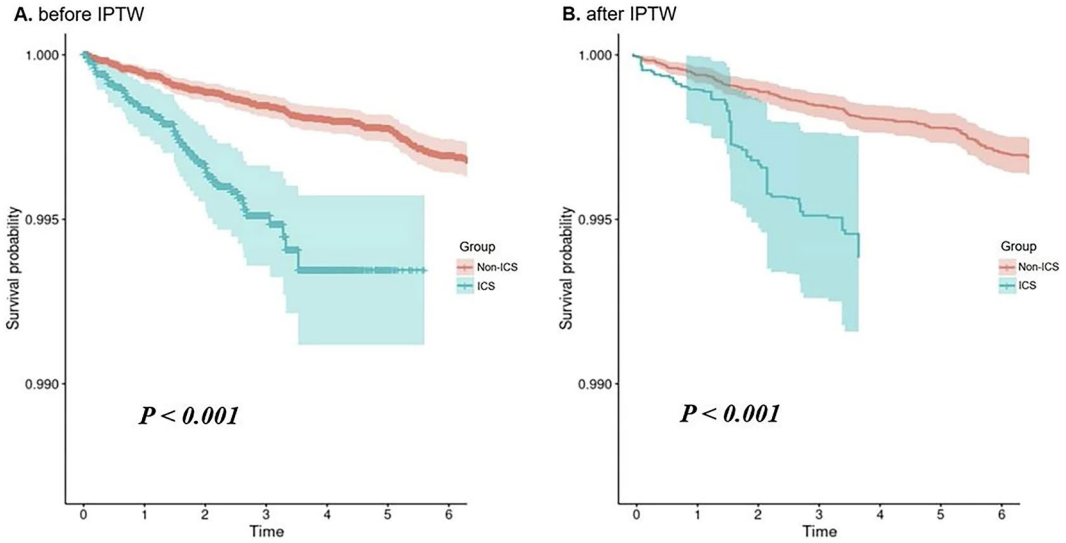

Fig. 3. Cumulative incidence of adrenal insufficiency. (A) Before IPTW matching, (B) After IPTW matching. The cumulative incidence of adrenal insufficiency (AI) was depicted using a Kaplan-Meier curve, with both the x-axis (follow-up duration in years) and y-axis (cumulative AI incidence) adjusted to scale. The curves represent ICS users (blue) and non-ICS users (red), with the statistical significance evaluated using the log-rank test (p-value provided in the figure). The shaded regions around the curves indicate the 95% confidence intervals, illustrating the variability in AI risk over time. ICS = inhaled corticosteroids; IPTW = inverse probability of treatment weighting.

Discussion

Our data suggest that ICS use is associated with an increased risk of developing AI in a nationwide population-based study. Although we observed a moderate dose-dependent relationship between the ICS dosage and AI risk, this association was particularly pronounced above a certain threshold. Furthermore, this association remained consistent across various subgroups, including age, smoking status, income level, and underlying airway diseases. However, it exhibited a more significant association in males, individuals with systemic steroid use, and those with high CCI scores. Our findings highlight the importance of balancing the benefits of ICS with the potential risks of AI, emphasizing the need for careful risk management and regular monitoring in high-risk subgroups. Using large-scale, real-world data, we confirmed the increased AI risk associated with ICS use and identified key areas for further investigation.

We found that ICS use increased the risk of AI in patients with chronic airway disease, consistent with previous findings[12–14]. Lapi et al. found that in a Canadian case-control study (1990–2005), high-dose ICS users had an increased risk of AI (odds ratio [OR]: 1.84, 95% CI: 1.16–2.90), although the overall AI rate in ICS users was not significantly higher[13]. A UK case-control study found that recent ICS use (within 90 days) was associated with AI (OR: 3.4, 95% CI: 1.9–5.9), but no link was observed with earlier ICS use[12]. A meta-analysis showed that while ICS had a lower absolute AI risk (7.8, 95% CI: 4.2–13.9) compared to oral (48.7) or intraarticular steroids (52.2), they were still linked to an increased AI risk[14]. However, other findings, particularly those from randomized controlled trials (RCTs), have been more mixed[16–18]. In a 52-week RTC with asthma children ($n = 187$), ICS use did not significantly impact cortisol levels[17], and similarly, ciclesonide showed no major effect on adrenal function biomarker in asthma adults ($n = 248$)[16]. However, fluticasone and beclomethasone were associated with notable cortisol suppression, as confirmed in multiple studies[16,18]. Despite these mixed results, our data suggest that all ICS types carry some degree of AI risk, reinforcing the importance of cautious long-term use.

However, our analysis found that ciclesonide, typically known for lower systemic effects due to rapid first-pass metabolism[35], showed a higher AI risk, while fluticasone had the lowest HR. This contrasts with the general understanding that fluticasone, with its high lipophilicity, prolonged half-life, and strong glucocorticoid receptor affinity, usually poses the highest systemic risk[36]. Despite using IPTW to minimize confounding, unmeasured factors may have contributed to the higher AI risk in ciclesonide users. Ciclesonide may have been preferentially prescribed to patients thought to be at lower risk of side effects, who may have had a higher baseline risk for AI, contributing to the observed outcomes.

ICS can suppress the HPA axis, leading to AI, particularly with long-term or high-dose use[37]. Prolonged and high-dose usage can lead to HPA deficiency, adrenal gland atrophy, and persistent adrenal suppression even after treatment cessation, lasting up to several years[38,39]. Kachroo et al. found that ICS use in asthma patients ($n = 661$) significantly reduced levels of key steroid metabolites, including dehydroepiandrosterone sulphate and cortisol, suggesting a potential association between ICS use and AI, with a global reduction in cortisol levels observed over a 24-hour period[40]. The symptoms AI, such as fatigue, headaches, weakness, poor growth, syncope, and low blood pressure, can make diagnosis more difficult. In addition, several paediatric asthma

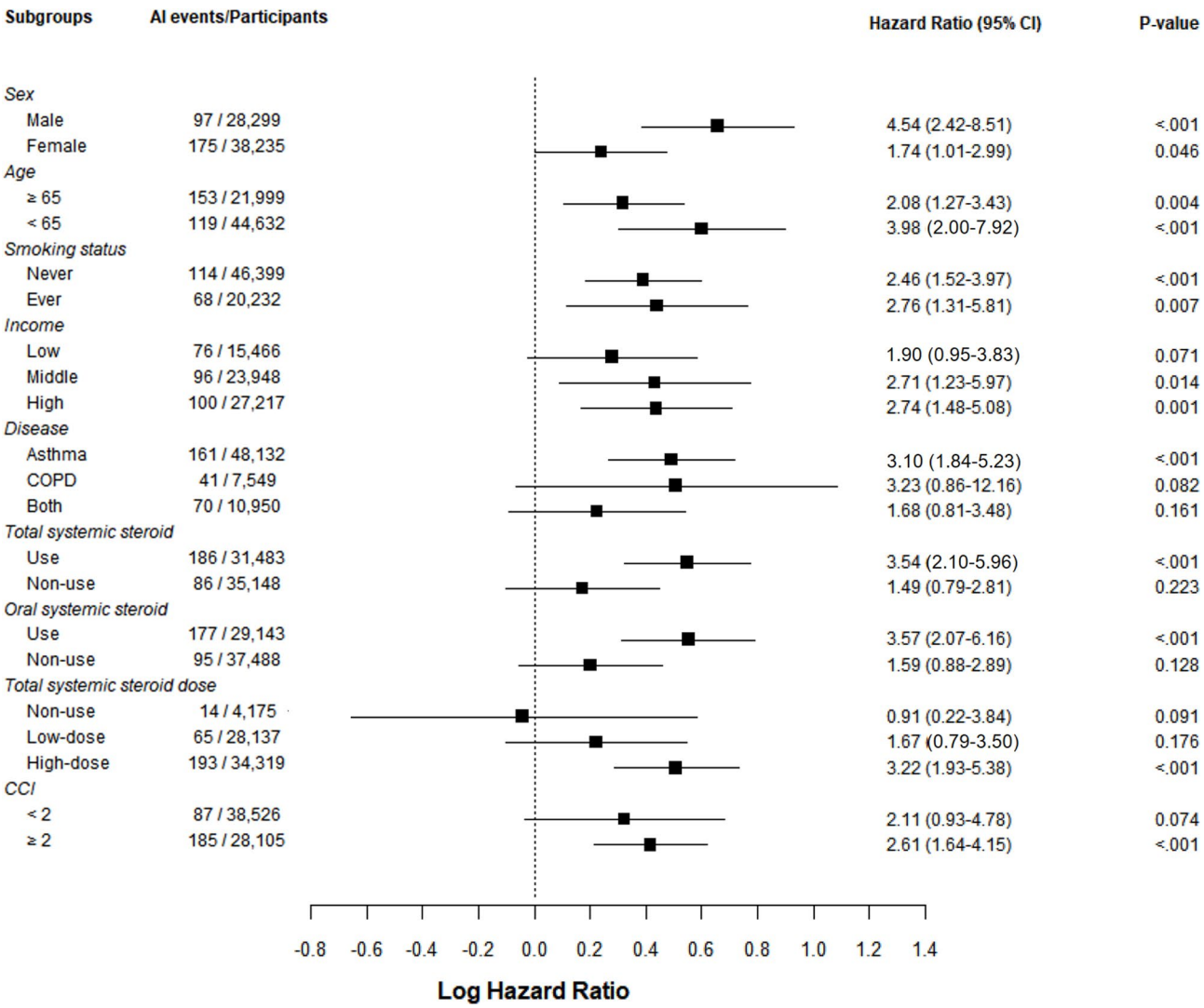

Fig. 4. Forest plot for the risk of adrenal insufficiency in subgroup analysis. In the plot, squares indicate the adjusted hazard ratios for ICS use, with horizontal lines denoting the 95% confidence intervals on a logarithmic scale. P-values are derived from comparisons with non-ICS users. COPD = chronic obstructive pulmonary disease; CCI = Charlson comorbidity index.

clinical guidelines recommend conducting AI screening tests when using ICS for six months or longer or at medium to high doses[41,42]. While the potential for AI associated with inhaled ICS use in adults has not received significant attention, our study indicates that ICS use increases the risk of AI, even in adult patients. Notably, ICS remains the first-line therapy for adult patients with asthma[43] and are recommended for use in patients with COPD accompanied by type 2 inflammation[44,45]. Goldbloom et al. demonstrated that among 46 paediatric patients with symptomatic AI, 80% were treated with ICS for asthma, with 32% of them receiving ICS therapy alone[46]. Furthermore, in our study, the intermittent use of ICS appeared to increase the risk of AI to a similar extent as that in continuous use. A study by Schütz et al. found that a 14-day regimen of systemic corticosteroids significantly suppressed the HPA axis in 8 out of 9 COPD patients not previously on systemic steroids, with effects lingering in 3 patients three weeks post-therapy[47]. This highlights the importance of monitoring for AI in adults using ICS or systemic steroids, even with intermittent use, not just prolonged continuous use.

The association between ICS use and AI was more pronounced in individuals with systemic steroid use, and those with a high CCI, consistent with previous findings[48]. Although no clear dose-dependent increase in AI risk was seen at higher ICS doses, continuous dose analysis showed a significant rise in AI occurrence, particularly at medium doses or when combined with systemic steroid use. In contrast, our study found a lower AI risk among those not using systemic steroids, highlighting the importance of monitoring AI in ICS users, especially those on systemic steroids. Routine AI screening for high-risk groups could allow for earlier detection and prevention of complications.

We observed a non-linear relationship between ICS dose and AI risk, with a non-significant association in the highest-dose group. While the exact mechanism is unclear, one possible explanation is that patients on higher doses may undergo more frequent medical monitoring, leading to earlier detection and management of

AI before it fully develops, thus reducing the risk. Another factor could be "survivor bias," where patients on high doses for extended periods might discontinue ICS before AI occurs, lowering the observed risk. Although we adjusted for several factors, including concurrent systemic steroid use, using IPTW, unmeasured confounders may still have influenced this trend. Lastly, the small sample size in the high-dose ICS group may have reduced statistical power, potentially explaining the lower observed risk. The low overall incidence of AI (1.69 per 1,000 ICS users, 0.54 per 1,000 overall) may have limited the statistical significance in categorical analyses. Further research is needed to explore these findings in greater detail.

Our findings emphasize the importance of monitoring AI in chronic airway disease patients using ICS, especially at medium-to-high doses or in high-risk subgroups. This evidence may guide treatment guidelines toward routine adrenal function testing in long-term ICS users. By incorporating large-scale real-world data, our study reinforces the need for balancing ICS benefits with associated risks and calls for refining AI screening and personalized dosing strategies based on individual risk factors.

Our study had several limitations. First, as it was a retrospective analysis of claims databases, it is susceptible to inherent bias, including selection bias, information bias, or confounding factors. To address this, we employed a propensity score analysis with IPTW to mitigate selection bias and control for potential confounders. IPTW minimizes group differences while preserving our full sample size, a key advantage over methods like propensity matching that restrict data to matched cases[26], thereby enhancing the strength and credibility of our results. Additionally, our study, conducted with a randomly sampled population from the Korean NHI, which covers the entire nation, likely has a lower possibility of selection bias. Second, the reliance on claims data limited the ability to assess direct clinical measures such as adherence to ICS therapy, exact dosing patterns over time, and clinical severity of adrenal insufficiency. In addition, claims data may not fully capture the nuances of disease progression or subclinical AI cases, potentially leading to misclassification or underreporting. Specifically, we could not track time-varying ICS doses, preventing the use of time-dependent Cox analysis. However, our results from the PH Cox model remain robust, as the PH assumption was satisfied. Future studies should incorporate prospective designs with direct clinical measures, including biomarkers of adrenal function, and precise dosing data that allow for time-varying analyses to validate these findings and enhance accuracy. Third, our findings may be specific to the Korean population, which limits their generalisability. Forth, we used diagnostic codes from claims databases, which may introduce systematic biases despite careful definitions of diseases and outcomes. To enhance validity, further large-scale studies using more accurate medical records are recommended. Fifth, our study included only patients who underwent health screenings, which may affect generalizability. However, in South Korea, health screenings are provided to all individuals every two years, making the inclusion relatively representative and minimizing concerns about generalizability. Sixth, despite the representativeness of the NHIS-NSC, the dataset has a limitation as claims database, excluding non-reimbursable treatments like plastic surgery. However, since most ICS and related respiratory medications analyzed were reimbursable, the impact is minimal. In addition, AI patients not registered in the NHID might have been excluded, but with 97.1% national coverage, this is unlikely to have significantly affected our findings. Lastly, the low incidence of AI, especially in smaller groups where HR exceeded 1 without statistical significance, may be due to limited statistical power from the small sample size. This necessitates cautious interpretation and indicates a need for further research with larger datasets. Despite these limitations, our comprehensive approach using a large claims database provides valuable insights into the association between ICS use and AI risk.

Conclusion

In summary, our study suggests a potential link between ICS use and increased risk of AI in patients with chronic airway disease based on large-scale, real-world data. However, this finding must be considered in light of potential confounders and the reliance on claims data. Although the overall risk of AI is low, monitoring and screening for AI, especially in adults using ICS along with systemic steroids for extended periods, are crucial. These findings underscore the importance of balancing ICS benefits with careful risk management in clinical practice and informing health policy. Further prospective or RCTs are needed to track ICS use and dose changes over time, assess AI risk across different ICS types and doses, and incorporate clinical data like biomarkers to better understand the association and develop strategies that minimize AI risk while effectively managing chronic airway diseases.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Hyewon Lee: Data curation (lead); formal analysis (lead); methodology (equal); software (lead); visualization (equal); writing – original draft (equal); writing – review and editing (equal). Hee-Young Yoon: Conceptualization (lead); data curation (equal); formal analysis (equal); funding acquisition (lead); investigation (equal);

methodology (equal); project administration (lead); resources (lead); software (equal); supervision (lead); validation (lead); visualization (equal); writing – original draft (equal); writing – review and editing (equal).

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
The study protocol was approved by the Institutional Review Board of the Soonchunhyang University Seoul Hospital (2023-06-008), and the requirement for informed consent was waived due to the de-identified nature of the NHIS-NSC dataset.

Consent for publication
Not applicable.

Additional information
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