EnM
ENDOCRINOLOGY AND METABOLISM

Original Article

Endocrinol Metab 2025;40:82-92
https://doi.org/10.3803/EnM.2024.1990
pISSN 2093-596X · eISSN 2093-5978

Elevated Fracture Risks in Patients Using Inhaled Corticosteroids: A Korean Nationwide Study

Sung Hye Kong[1,2,*], Ae Jeong Jo[3,*], Chan Mi Park[4], Kyun Ik Park[4], Ji Eun Yun[4], Jung Hee Kim[2,5]

[1]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam; [2]Department of Internal Medicine, Seoul National University College of Medicine, Seoul; [3]Department of Data Science, Andong National University, Andong; [4]National Evidence-Based Healthcare Collaborating Agency (NECA); [5]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

Background: In this comprehensive retrospective nationwide cohort study, we examined the relationships between various asthma medications and bone health, utilizing data from the National Health Insurance Service database of South Korea.

Methods: From 2015 to 2019, the relevant dataset included 168,611 individuals aged 66 years, among whom 8,747 were diagnosed with asthma. We focused on a subset of 6,173 patients, all 66-year-old women. Participants were categorized into four groups: non-users of asthma medication (n=2,868), leukotriene antagonist users (n=2,281), inhaled corticosteroid (ICS) users (n=517), and those using a combination of ICS and long-acting beta-agonist (ICS+LABA) medication (n=507). The primary outcomes measured were the incidences of major osteoporotic fractures and hip fractures during the follow-up period.

Results: Over 2.7 years of follow-up, 615 cases of major osteoporotic fractures and 96 cases of hip fractures were recorded. ICS users exhibited a heightened risk of both injuries, with hazard ratios of 1.38 (95% confidence interval [CI], 1.18 to 1.63; P<0.001) for major osteoporotic fractures and 1.56 (95% CI, 1.33 to 1.83; P<0.001) for hip fractures. Similarly elevated risks were observed in the ICS+LABA group. Notably, the risk associated with ICS was particularly pronounced among patients with osteopenia for both fracture types. Overall, the use of ICS, alone or in combination with LABA, in patients with asthma is associated with significantly increased risks of osteoporotic fractures, especially among those with osteopenia.

Conclusion: These findings underscore the importance of considering bone health when managing asthma, especially in older patients and those with existing bone density issues.

Keywords: Asthma; Fracture; Osteoporosis; Inhaled corticosteroids

Received: 24 March 2024, **Revised:** 13 May 2024, **Accepted:** 10 June 2024

Corresponding authors: Jung Hee Kim
Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-4839, **Fax:** +82-2-2072-4839, **E-mail:** jhee1@snu.ac.kr

Ji Eun Yun
Division of Healthcare Technology Assessment Research, National Evidence-Based Healthcare Collaborating Agency, 400 Neungdong-ro, Gwangjin-gu, Seoul 04933, Korea
Tel: +82-2-2174-2754, **Fax:** +82-2-741-7160, **E-mail:** jeyun@neca.re.kr

*These authors contributed equally to this work.

INTRODUCTION

Asthma is a prevalent condition affecting a significant portion of the global population [1]. This disease often requires long-term pharmacological intervention to manage symptoms and improve quality of life [2]. However, the medications used for treatment can have systemic effects that may impact other aspects of health, including bone integrity [3].

Bone health is a growing concern among healthcare providers, particularly for aging populations, who are particularly susceptible to conditions such as osteoporosis and fractures [4,5]. These bone-related issues pose serious health risks and meaningfully impact healthcare costs and patient morbidity [6]. Therefore, it is crucial to investigate factors that may exacerbate or mitigate these risks, especially in populations already at risk of poor bone health.

Various medications are available for the management of asthma, including inhaled corticosteroid (ICS), long-acting beta-agonist (LABA), and leukotriene antagonist (LTA), among others [7]. While these treatments are effective for airway management, they have different systemic effects that may impact bone metabolism and health [3,8,9]. Previous studies have examined the association between corticosteroid use and reduced bone mineral density (BMD) [8,10], but only limited research has explored the risk of fractures across multiple types of asthma medications, particularly LTA and/or LABA [11].

The National Health Insurance Service (NHIS) database of South Korea represents an extensive resource for examining health-related issues on a nationwide scale [12]. Over the past decade, this database has captured approximately 97.2% of the South Korean population and features rich datasets that include patient demographics, medical prescriptions, and comorbidities. The National Screening Program for Transitional Ages (NSPTA) further augments these data by conducting BMD testing, facilitating an in-depth analysis of bone health.

This study was performed to investigate the relationships between various types of asthma medications and bone health, focusing on the risk of fractures. Patients from the NHIS database were categorized into groups according to medication use: nonusers, LTA users, ICS users, and those using a combination of ICS and LABA. By examining the issue from multiple perspectives, this study sought to fill gaps in our understanding of the systemic effects of asthma medications, particularly about bone health.

METHODS

Data source

The study employed a nationwide retrospective design, utilizing data collected from the NHIS database of South Korea from 2015 to 2019 [13,14]. Managed by the Korean government, this insurance program covers approximately 97.2% of the population and provides a wealth of healthcare reimbursement information, including patient demographics, medical prescriptions, diagnoses, and associated costs. The NSPTA, initiated in 2007, administered BMD tests to 66-year-old women, primarily using dual-energy X-ray absorptiometry for spine or femoral neck measurements when spinal assessments were not feasible [15,16]. For longitudinal follow-up, each participant was assigned an anonymized personal identification number. The Institutional Review Board of the National Evidence-Based Healthcare Collaborating Agency (NECA) approved this study (IRB No. 20-004). Due to the anonymization of the data, the requirement for informed consent was waived. The National Research Foundation of Korea and NECA provided funding for this research.

Study population

Between January 1, 2015 and December 31, 2016, a total of 168,611 individuals aged 66 years underwent NSPTA health examinations. These patients underwent follow-up until December 31, 2019. From this group, 8,747 individuals who were diagnosed with asthma after the index date (defined as the date of the BMD screening) were initially selected. A participant was considered to have asthma if they were diagnosed with an International Classification of Diseases, 10th Revision (ICD-10) code of J45 or J46 at least twice. From the selected individuals, 876 patients diagnosed with rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, or inflammatory bowel disease were excluded from the study. Additionally, 1,049 patients who were treated with medications other than LTA, ICS, or a combination of ICS and LABA, or who had received osteoporosis medications before the index date, were excluded. Furthermore, 649 patients were excluded due to the absence of test results caused by system errors. Following these steps, 6,173 individuals remained and were included in the final analysis (Fig. 1). Baseline clinical characteristics and study eligibility were determined 1 year before the index date.

Patients were included in a specific medication group if they had consistently used the same medication or combination for over a year, maintaining the same regimen from the index date until the end of the follow-up period. This inclusion criterion

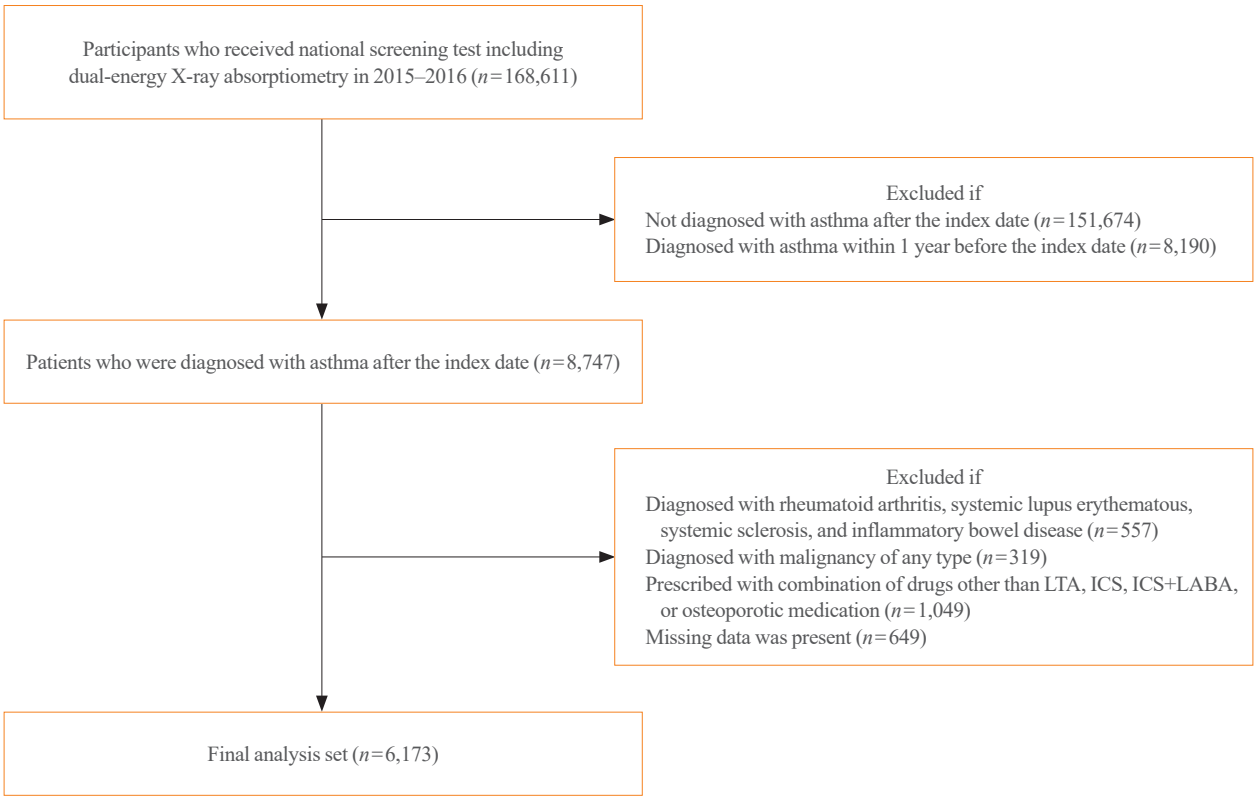

Fig. 1. Selection of study participants. LTA, leukotriene antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist.

was established to ensure the stability of the treatment variables and to minimize the influence of changes in regimen on the study outcomes. Anatomical Therapeutic Chemical codes for the medications are presented in Supplemental Methods. Other combinations of medications, including LABA only, short-acting beta-agonists only, long-acting anticholinergics (LAMA) only, LAMA+LABA, and biologics including omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab were excluded due to the limited numbers of patients who remained on these specific combinations for over a year.

Operational definitions of fracture outcomes

The primary outcomes were major osteoporotic and hip fracture events, as defined by ICD-10 diagnostic codes, that occurred during the follow-up period. Major osteoporotic fracture events were specified as hospital visits on two or more occasions after the index date due to the following diagnostic codes: S22.0, S22.1, S32.0, M48.4, M48.5, S42.2, S42.3, S52.5, S52.6. These visits could be to either the admission or the outpatient department. Hip fracture events were characterized by more than one hospital visit after the index date for the relevant diagnostic codes (S72.0, S72.1) to either the admission or outpatient department, accompanied by more than one corresponding treatment code (N0601, N0611, N0305, N0981, N0641, N0652, N0654, N0711, N0715). The follow-up period extended from the date of cohort entry until the occurrence of a fragility fracture, a change in the drug combination for asthma, death, or the end of the study period on December 31, 2019, whichever came first.

Operational definitions of clinical variables

The history of fractures, diabetes mellitus, cardiovascular diseases, cerebrovascular diseases, chronic renal failure, and malignancy was ascertained using diagnostic codes. To ensure the accuracy of diagnosis, conditions were considered present if a participant had received treatment for the specific condition on two or more occasions. These conditions included diabetes mellitus (codes E10–E14), cardiovascular diseases (codes I20–I22), cerebrovascular diseases (codes I63, I64, I693, I694, G45, I60–62, I690–692), chronic renal failure (codes N183, N184, N185, N258, Z491, Z492, Z940), chronic liver disease (code K746), Parkinson disease (code G20), dementia (codes F00.x–F03.x, F05.1, G30.x, G31.1), and malignancy (all C codes). The Charlson Comorbidity Index was calculated using the methodology described in previous research [17]. Individuals were classified

as oral steroid users if they had been exposed to glucocorticoids chronically, defined as a daily dose of ≥5 mg of prednisolone-equivalent steroid for a duration of ≥3 months.

Body mass index (BMI) was measured on the entry date. Data were collected on the participant's history of falls, social history (including smoking and drinking patterns), and physical activity (PA) through standardized self-administered questionnaires. Ever-smokers were categorized as individuals who were either ex-smokers or current smokers. Drinkers were defined as those who consumed alcohol more than once per week. Baseline PA was assessed using the International Physical Activity Questionnaire, which evaluates mode, frequency, and intensity of activity [18]. Activity was further classified according to its intensity: walking, moderate, or vigorous. Moderate PA was characterized by a slight increase in breathing or heart rate, or by a perception of fairly hard exertion, such as carrying light loads, slow cycling, or brisk walking. Vigorous PA was associated with a substantial increase in breathing or heart rate, or a perception of moderately hard exertion, and included activities such as carrying heavy loads, fast cycling, running, mountain climbing, playing soccer, or engaging in similar activities. Moderate-to-vigorous PA was defined as engaging in moderate or vigorous PA at least once per week over the past 6 months. Participants' incomes on the index date were assessed using data on NHIS insurance premiums. Annual income levels were categorized into five groups based on quintile ratios.

Statistical analyses

Continuous data are presented as mean±standard deviation, while categorical data are reported as number (percentage). Participant characteristics were compared across groups using the Student *t* test for continuous variables and the chi-square test for categorical variables. Cox proportional hazards regression models were applied to the four medication groups (non-users, LTA users, ICS users, and ICS+LABA users) to estimate the β coefficients, hazard ratios (HRs), and 95% confidence intervals (CIs) for major osteoporotic and hip fractures, considering death as a competing risk using the Fine and Gray model [19]. The survival time was calculated from the date of cohort entry until the occurrence of fractures, a change in the asthma drug combination, death, or December 31, 2019, whichever came first.

To compare the four groups, an inverse probability of treatment weighting (IPTW) analysis was applied with stabilized weights derived from propensity scores [20]. The propensity for each group was calculated using a logistic regression model with baseline covariates, including BMD, smoking status, PA, history of falls and fractures, BMI, income level, oral steroid use, and comorbidities (diabetes mellitus, cerebrovascular disease, cardiovascular disease, cancer, chronic kidney disease, liver failure, and dementia). To evaluate the balance of baseline characteristics across groups, the maximum absolute standardized difference (ASD) was calculated for each covariate. An ASD of ≤0.1 was considered to indicate a negligible difference in the covariate among groups [21]. The risk of fractures in the four groups was determined using weighted Cox proportional hazards regression models with IPTW. HRs are presented with non-users serving as the reference group. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Clinical characteristics of patients by medication(s) used

In the study cohort of 6,173 patients, we analyzed clinical characteristics according to the type of medication used: no asthma medication (classified as non-users, n=2,868), LTA (n=2,281), ICS (n=517), and ICS+LABA (n=507) (Table 1). The distribution of patients with normal BMD, osteopenia, and osteoporosis did not significantly differ across medication categories (P=0.057). The highest prevalence of osteopenia was observed among non-users (45.3%), whereas the ICS+LABA group had the highest prevalence of normal BMD (20.7%). Smokers were significantly more prevalent in the ICS+LABA group than in the other categories (5.7%, P=0.015). No significant difference was observed in the proportion of current drinkers between groups (P=0.285). Furthermore, across the medication categories, no significant differences were found in the prevalence of moderate-to-severe PA or history of falls. The prevalence of cancer was significantly higher in the ICS+LABA group than in the other groups (2.7%, P=0.002). The incidence of other comorbidities was similar across categories. The ICS+LABA group included the highest proportion of patients using oral steroids, a significant finding (3.1%, P=0.001). The follow-up duration was shortest in the ICS group (2.59±0.69 years) and differed significantly among the groups (P<0.001).

Risks of major osteoporotic and hip fractures by medication(s) used

Over the follow-up period of 2.7 years, 615 cases of major osteoporotic fractures and 96 cases of hip fractures occurred. After adjusting for confounders using the IPTW method (Table 2), the

Table 1. Clinical Characteristics of Patients by Medication(s) Used

Characteristic	Total (*n*=6,173)	Non-user (*n*=2,868)	LTA (*n*=2,281)	ICS (*n*=517)	ICS+LABA (*n*=507)	*P* value
BMI, kg/m^2						
<18.5	92 (1.4)	45 (1.5)	27 (1.1)	11 (2.1)	9 (1.7)	0.130
≥18.5, <23	1,574 (25.5)	722 (25.1)	604 (26.5)	135 (26.1)	113 (22.2)	
≥23, <25	1,618 (26.2)	748 (26.0)	617 (27.0)	136 (26.3)	117 (23.0)	
≥25, <30	2,444 (39.5)	1,161 (40.4)	865 (37.9)	197 (38.1)	221 (43.5)	
≥30	445 (7.2)	192 (6.6)	168 (7.3)	38 (7.3)	47 (9.2)	
Income level, percentile (*n*=5,777)						
≤20	1,000 (16.2)	494 (17.5)	363 (16.2)	69 (13.6)	74 (14.8)	0.586
21–40	661 (10.7)	303 (10.7)	242 (10.8)	57 (11.2)	59 (11.8)	
41–60	845 (13.6)	403 (14.3)	299 (13.4)	65 (12.8)	78 (15.6)	
61–80	1,517 (24.5)	686 (24.3)	583 (26.1)	134 (26.5)	114 (22.9)	
≥81	1,754 (28.4)	812 (28.8)	641 (28.7)	154 (30.5)	147 (29.5)	
BMD category						
Normal BMD	1,127 (18.2)	477 (16.6)	442 (19.3)	103 (19.9)	105 (20.7)	0.057
Osteopenia	2,732 (44.2)	1,301 (45.3)	989 (43.3)	214 (41.3)	228 (44.9)	
Osteoporosis	2,314 (37.4)	1,090 (38.0)	850 (37.2)	200 (38.6)	174 (34.3)	
Ever-smoker	218 (3.5)	96 (3.3)	82 (3.5)	11 (2.1)	29 (5.7)	0.015
Current drinker	568 (9.2)	283 (9.8)	203 (8.9)	39 (7.5)	43 (8.4)	0.285
Moderate-to-vigorous PA	44 (0.7)	22 (0.7)	16 (0.7)	3 (0.5)	3 (0.5)	0.949
History of fall	5,703 (92.3)	2,665 (92.2)	2,096 (91.8)	470 (90.9)	472 (93.1)	0.268
History of fracture	308 (4.9)	139 (4.8)	106 (4.6)	29 (5.6)	34 (6.7)	0.234
Diabetes mellitus	1,495 (24.2)	688 (23.9)	555 (24.3)	128 (24.7)	124 (24.4)	0.978
Cerebrovascular disease	337 (5.4)	145 (5.0)	137 (6.01)	29 (5.6)	26 (5.1)	0.501
Cardiovascular disease	669 (10.8)	293 (10.2)	252 (11.0)	56 (10.8)	68 (13.4)	0.192
Cancer	116 (1.8)	34 (1.1)	56 (2.4)	12 (2.3)	14 (2.7)	0.002
CKD	63 (1.0)	27 (0.9)	19 (0.8)	8 (1.5)	9 (1.7)	0.154
Liver failure	24 (0.3)	17 (0.5)	7 (0.3)	0	0	0.058
Dementia	135 (2.1)	59 (2.0)	46 (2.0)	11 (2.1)	19 (3.7)	0.097
Parkinson disease	138 (2.2)	67 (2.3)	48 (2.1)	11 (2.1)	12 (2.4)	0.944
CCI score						
0	1,621 (26.2)	762 (26.5)	589 (25.8)	142 (27.4)	128 (25.2)	0.224
1	1,791 (29.0)	872 (30.4)	635 (27.8)	134 (25.9)	150 (29.5)	
2	1,226 (19.8)	554 (19.3)	473 (20.7)	109 (21.0)	90 (17.7)	
≥3	1,535 (24.8)	680 (23.7)	584 (25.6)	132 (25.5)	139 (27.4)	
Oral steroid user	82 (1.3)	23 (0.8)	35 (1.5)	8 (1.5)	16 (3.1)	0.001
Follow-up duration, yr	2.81±0.66	2.87±0.64	2.80±0.67	2.59±0.69	2.70±0.67	<0.001

Values are expressed as number (%) or mean±standard deviation. Due to the characteristics and timeframe of the data, all patients were 66-year-old women. Moderate-to-vigorous PA was defined as reporting moderate or vigorous activity at least once per week during the prior 6 months. Steroid users were defined as patients who had received oral glucocorticoids for more than 3 months at a dose of at least 5 mg prednisolone-equivalent steroid daily over the past year. Comparisons between groups were analyzed using the Student *t* test for continuous variables and the chi-square test for categorical variables. The analysis of income level included 5,777 participants, after excluding 396 participants for whom these data were not available.
LTA, leukotriene antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; BMI, body mass index; BMD, bone mineral density; PA, physical activity; CKD, chronic kidney disease; CCI, Charlson Comorbidity Index.

HRs for major osteoporotic and hip fractures were evaluated across medication groups. Compared to non-users, those taking asthma drugs had a significantly higher adjusted risk of major osteoporotic fractures, with an HR of 1.16 (95% CI, 1.15 to 1.16; $P<0.001$). The HR for hip fractures among asthma drug users was 1.07 (95% CI, 1.06 to 1.07; $P<0.001$) compared to non-users (Supplemental Fig. S1). ICS users exhibited a significantly elevated risk of both major osteoporotic and hip fractures, with HRs of 1.38 (95% CI, 1.18 to 1.63; $P<0.001$) and 1.56 (95% CI, 1.33 to 1.84; $P<0.001$), respectively. Similarly, users of ICS combined with LABA also demonstrated a significantly higher risk of both fracture types, with HRs of 1.46 (95% CI, 1.33 to 1.73; $P<0.001$) for major osteoporotic fractures and 1.38 (95% CI, 1.18 to 1.61; $P<0.001$) for hip fractures (Fig. 2). When LTA users were used as the reference, the IPTW-adjusted risks for ICS and ICS+LABA users remained significantly higher. The HRs for major osteoporotic fractures were 1.51 (95% CI, 1.30 to 1.76; $P<0.001$) for ICS users and 1.34 (95%

Table 2. IPTW-Adjusted Risk of Major Osteoporotic and Hip Fractures by Medication(s) Used

Group	Major osteoporotic fracture			Hip fracture		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Non-user (*n*=2,868)	Ref			Ref		
User (*n*=3,305)	1.16	1.15–1.16	<0.001	1.07	1.06–1.07	<0.001
Non-user (*n*=2,868)	Ref			Ref		
LTA (*n*=2,281)	1.04	0.87–1.24	0.683	1.03	0.87–1.23	0.680
ICS (*n*=517)	1.38	1.18–1.63	<0.001	1.56	1.33–1.84	<0.001
ICS+LABA (*n*=507)	1.46	1.33–1.73	<0.001	1.38	1.18–1.61	<0.001
LTA (*n*=2,281)	Ref			Ref		
ICS (*n*=517)	1.51	1.30–1.76	<0.001	1.67	1.21–2.30	0.001
ICS+LABA (*n*=507)	1.34	1.15–1.56	0.001	1.78	1.30–2.44	0.001

Cox regression analysis with IPTW was performed.
IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; LTA, leukotriene antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist.

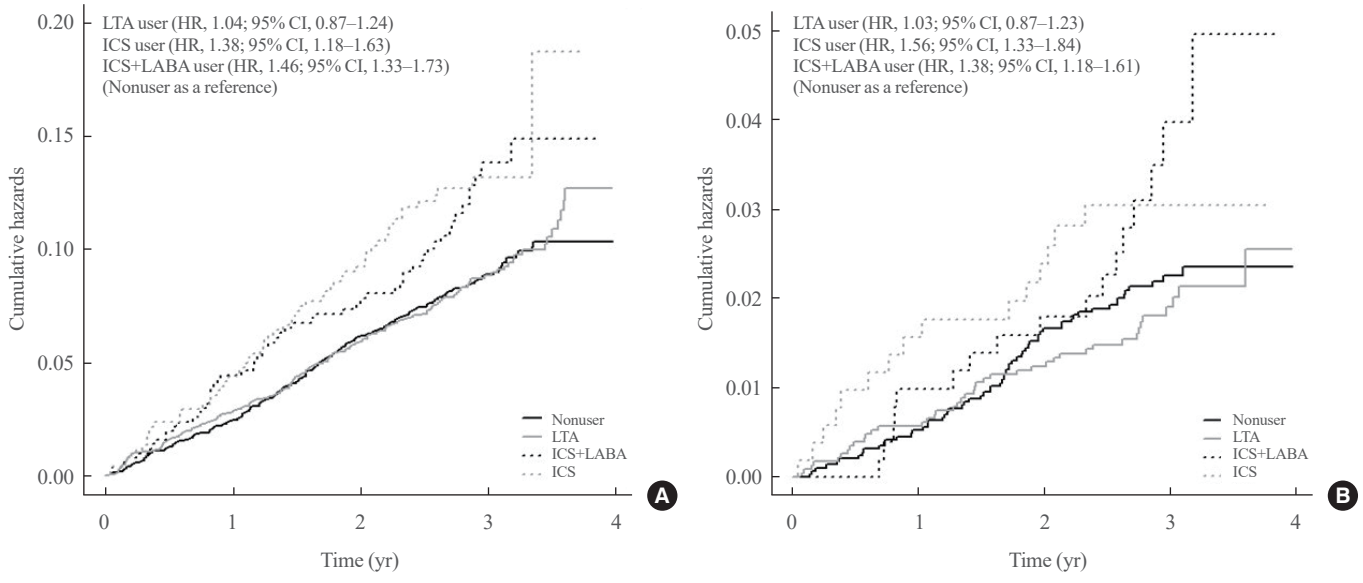

Fig. 2. Risk of major (A) osteoporotic fracture and (B) hip fracture in patients with asthma by medication(s) used. LTA, leukotriene antagonist; HR, hazard ratio; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist.

CI, 1.15 to 1.56; *P*=0.001) for ICS+LABA users. For hip fractures, the HRs were 1.67 (95% CI, 1.21 to 2.30; *P*=0.001) for ICS and 1.78 (95% CI, 1.30 to 2.44; *P*=0.001) for ICS+LABA. In summary, the IPTW-adjusted analysis suggests that the use of ICS, either alone or in combination with LABA, is associated with significantly elevated risk of major osteoporotic and hip fractures. In contrast, LTA use does not appear to significantly affect the risk of these outcomes. The results of the unadjusted analyses are presented in Supplemental Table S1.

Subgroup analysis according to BMD

Subgroup analysis stratified by BMD revealed differences in the risk of major fractures across the various medication groups. Within all three BMD subgroups, the risk of major osteoporotic and hip fractures was similar for medication users in general compared to non-users. However, among individuals with normal BMD, those taking ICS had a significantly higher risk of both major osteoporotic fractures (HR, 1.83; 95% CI, 1.31 to 2.57; *P*=0.001) and hip fractures (HR, 2.90; 95% CI, 1.61 to 5.19; *P*=0.001) than the reference group of non-users. For users of LTA and ICS+LABA, the risks did not differ significantly from those in the reference group (Table 3).

In the osteopenia subgroup, individuals using ICS demonstrated a significantly increased risk of both major osteoporotic fractures (HR, 1.27; 95% CI, 1.05 to 1.53; *P*=0.010) and hip fractures (HR, 2.04; 95% CI, 1.45 to 2.87; *P*<0.001) compared to non-users. Furthermore, those using combined ICS and LABA therapy also exhibited significantly elevated risks for both fracture types.

In individuals with osteoporosis, the use of ICS and ICS+LABA was associated with a significantly increased risk of major osteoporotic fractures (HR, 1.30; 95% CI, 1.09 to 1.55; *P*=0.003 and HR, 1.48; 95% CI, 1.24 to 1.76; *P*<0.001, respectively), but not hip fractures. In comparison, LTA users exhibited a decreased risk of hip fractures (HR, 0.64; 95% CI, 0.43 to 0.98; *P*=0.039). In summary, fracture risk varied considerably depending on BMD status and the type of medication used. ICS and ICS+LABA users generally demonstrated an elevated risk, particularly among patients with osteopenia.

Table 3. Subgroup Analysis according to BMD

BMD group	Medication group	Major osteoporotic fracture			Hip fracture		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Normal	Non-user (*n*=477)	Ref			Ref		
	User (*n*=650)	1.31	0.92–1.88	0.143	1.62	0.85–3.07	0.135
	Non-user (*n*=477)	Ref			Ref		
	LTA (*n*=442)	1.17	0.81–1.70	0.391	1.48	0.77–2.84	0.228
	ICS (*n*=103)	1.83	1.31–2.57	0.001	2.90	1.61–5.19	0.001
	ICS+LABA (*n*=105)	1.38	0.95–1.99	0.077	0.71	0.33–1.55	0.400
Osteopenia	Non-user (*n*=1,301)	Ref			Ref		
	User (*n*=1,431)	1.19	0.93–1.43	0.059	1.39	0.97–1.99	0.072
	Non-user (*n*=1,301)	Ref			Ref		
	LTA (*n*=989)	1.09	0.90–1.31	0.349	1.18	0.81–1.72	0.365
	ICS (*n*=214)	1.27	1.05–1.53	0.010	2.04	1.45–2.87	<0.001
	ICS+LABA (*n*=228)	1.66	1.39–1.98	<0.001	1.85	1.30–2.61	0.001
Osteoporosis	Non-user (*n*=1,090)	Ref			Ref		
	User (*n*=1,224)	1.14	0.95–1.36	0.145	0.81	0.55–1.20	0.311
	Non-user (*n*=1,090)	Ref			Ref		
	LTA (*n*=850)	1.02	0.85–1.23	0.801	0.64	0.43–0.98	0.039
	ICS (*n*=200)	1.30	1.09–1.55	0.003	1.00	0.69–1.47	0.966
	ICS+LABA (*n*=174)	1.48	1.24–1.76	<0.001	1.34	0.93–1.93	0.108

Cox regression analysis with inverse probability of treatment weighting was performed.
BMD, bone mineral density; HR, hazard ratio; CI, confidence interval; LTA, leukotriene antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist.

DISCUSSION

In this study, we conducted a multidimensional analysis of a Korean nationwide cohort to explore the association between asthma medication use and the risk of major osteoporotic and hip fractures. We found that the use of ICS, both alone and in combination with LABA, was associated with an increased risk of major osteoporotic and hip fractures compared to non-users or those taking LTA alone. Interestingly, among those taking both ICS and LABA, subgroup analysis revealed an elevated risk of hip fractures only in patients with osteopenia, and not in those with normal BMD or osteoporosis. These results suggest that ICS and ICS+LABA use may be significant risk factors for fractures and that fracture risk can vary based on BMD status.

The association between the use of ICS and an elevated risk of both major osteoporotic and hip fractures was a particularly striking finding of this study. These results align with previous research that has indicated a potential loss of BMD associated with prolonged corticosteroid use [22-26]. Multiple studies have reported dose-dependent decreases in BMD among patients with asthma [22,23]. Furthermore, a meta-analysis revealed a dose-response relationship with ICS use among patients with asthma, as the risk of non-vertebral fractures increased with a relative risk of 1.12 for every 1,000 g/day increase in inhaled beclomethasone [24]. Another recent meta-analysis yielded similar conclusions [26]. The underlying mechanisms connecting corticosteroids to bone health include the inhibition of osteoblast activity, the stimulation of osteoclast activity [24], and the disruption of bone remodeling [27]. A notable aspect of our study is the incorporation of risk stratification based on BMD, particularly for patients with osteopenia or normal BMD. For these individuals, the HRs for major osteoporotic and hip fractures are especially concerning. This suggests that even patients who do not fall within the osteoporotic BMD range face an increased risk for fractures in their old age if they use ICS for more than a year. Consequently, our results may provide a basis for recommending regular fracture risk assessments in patients on long-term ICS therapy and the adoption of preventative strategies.

Inhaled bronchodilators may have a synergistic effect on the anti-inflammatory response of ICS drugs [28]. Our study revealed that the combined use of ICS and LABA was associated with an increased risk of fractures compared to non-users or those using LTA alone. This finding complicates the discussion, as it previous research suggested that LABAs can support the anti-inflammatory effects of ICS by mechanisms such as augmented glucocorticoid receptor nuclear translocation [29]. Furthermore, continuous treatment with a low-dose β-agonist has been shown to decrease bone mass by increasing bone resorption without suppressing bone formation [30]. In a separate study, the beta-adrenergic receptor was found to be expressed in osteoblasts, and its activation led to a decrease in alkaline phosphatase expression levels *in vitro* [31]. Consequently, the synergistic interaction between ICS and LABA may inadvertently exacerbate adverse systemic effects on bone metabolism. Nonetheless, it is difficult to definitively conclude that the combination of ICS and LABA poses a higher fracture risk than ICS alone. This may stem in part from the lower dose of ICS used in the combination group compared to the ICS-only group. Additionally, although we adjusted for this in the IPTW analysis, the ICS+LABA group had a higher prevalence of ever-smokers, which could have contributed to the observed increased risks for major osteoporotic and hip fractures in this group. The results of our study highlight the need for further research to explore the interaction between ICS and LABA on bone metabolism and fracture risk.

In this study, patients using LTA medications did not exhibit an increased risk of fractures compared with non-users or those using other medications. Furthermore, among a subgroup of patients with osteoporosis, those using LTA showed a decreased risk of hip fracture compared to non-users. The differential in fracture risk between LTA users and other groups may be attributable to the mechanisms by which these medications function. LTA drugs block the action of leukotrienes, inflammatory mediators that are part of the eicosanoid family [32,33]. The bronchoconstriction caused by leukotrienes is crucial in the pathophysiology of asthma, justifying the use of LTA in treating asthma and similar airway diseases [34]. Leukotriene B4 has been found to inhibit osteoblastic cell proliferation in a dose-dependent manner [35], suggesting that LTA might have a beneficial impact on bone health, in contrast to other drugs such as ICS or β-agonists. Additionally, LTA medications have been shown to promote endochondral bone formation during fracture repair [36]. However, no evidence has yet indicated that the use of LTA in patients with asthma is associated with a reduced risk of fractures, warranting further research. Notably, despite using IPTW to adjust for underlying diseases and anthropometric measures—such as body weight—across the groups, the patients on LTA alone may have had less severe disease and, consequently, a lower risk of fractures.

The primary strengths of this study lie in its nationwide scope and large sample size. Our use of a national health database

from South Korea, which covers nearly the entire population, lends the findings considerable reliability and relevance for a wide-ranging audience. Furthermore, the NSPTA provides BMD measurements, allowing us to stratify the effects of each medication based on bone health status. To minimize bias from factors like underlying diseases or lifestyle differences, we employed IPTW, improving the reliability of our results. Additionally, our comparison of various medication types, including LTA, LABA, and ICS, offered more profound insights into the impact of each medication on bone health.

However, this study has several limitations. First, due to data constraints, we were unable to include dose-relationship information and details on symptom severity or pulmonary function, which limited our ability to fully reflect disease severity in the analysis. Second, the absence of a control group and the omission of the effects of symptom-relief medications may have influenced the outcomes. Third, the retrospective design of the study means that we cannot definitively establish causality and temporal relationships among medication use, BMD status, and fracture risk. Fourth, the relatively short follow-up period of 2.7 years and the specific focus on 66-year-old women may restrict the long-term and demographic generalizability of our findings. Additionally, the use of broad categories for bone health without detailed bone density values may not entirely capture the impacts of each medication type. The exclusion of key biochemical markers due to data limitations, including parathyroid hormone and vitamin D, could also affect the interpretation of the findings. Furthermore, limited data access precluded adjustment for specific cancer types, and the analysis was instead adjusted for the presence of any cancer. This limitation may have influenced the results. While our study defined major osteoporotic fractures as those occurring in the vertebra, hip, ankle, and wrist, we acknowledge that this does not cover all potential fracture sites, such as the pelvic bones. Additionally, certain relevant ICD-10 codes, such as M808 (age-related osteoporosis with current pathological fracture, vertebra) and S327 (multiple fractures of lumbar spine and pelvis), were not included. The exclusion of these codes is a limitation of our study, as it may lead to an underestimation of the full spectrum of osteoporotic fractures. These gaps highlight the need for future research to comprehensively investigate these aspects.

In conclusion, this study reveals a significant association between the use of ICS and the combination of ICS and LABA with an elevated risk of fractures in patients with asthma, particularly those with osteopenia. These findings underscore the need for an integrated treatment approach that encompasses not only respiratory management but also the monitoring and mitigation of fracture risks. To make informed prescription decisions, medical practitioners must be aware of these implications, particularly when managing chronic respiratory conditions in older adults and individuals with existing conditions like osteopenia or osteoporosis.

CONFLICTS OF INTEREST

Jung Hee Kim is a deputy editor of the journal. But she was 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.

ACKNOWLEDGMENTS

This study was funded by the National Research Foundation of Korea (2020R1A2C2011587, 2021R1A2C2003410) and the National Evidence-Based Healthcare Collaborating Agency (NA20-008).

The data in this study are open-source and provided by the National Health Insurance Service.

AUTHOR CONTRIBUTIONS

Conception or design: S.H.K., J.E.Y., J.H.K. Acquisition, analysis, or interpretation of data: A.J.J. Drafting the work or revising: S.H.K., A.J.J., C.M.P., K.I.P., J.E.Y., J.H.K. Final approval of the manuscript: S.H.K., A.J.J., C.M.P., K.I.P., J.E.Y., J.H.K.

ORCID

Sung Hye Kong *https://orcid.org/0000-0002-8791-0909*
Ae Jeong Jo *https://orcid.org/0000-0003-1228-7021*
Ji Eun Yun *https://orcid.org/0000-0003-2538-594X*
Jung Hee Kim *https://orcid.org/0000-0003-1932-0234*

REFERENCES

1. Beran D, Zar HJ, Perrin C, Menezes AM, Burney P; Forum of International Respiratory Societies working group collaboration. Burden of asthma and chronic obstructive pulmonary disease and access to essential medicines in low-income and middle-income countries. Lancet Respir Med 2015;3:159-70.
2. Wang J, Wang P, Shao Y, He D. Advancing treatment strate-

gies: a comprehensive review of drug delivery innovations for chronic inflammatory respiratory diseases. Pharmaceutics 2023;15:2151.
3. Heffler E, Madeira LN, Ferrando M, Puggioni F, Racca F, Malvezzi L, et al. Inhaled corticosteroids safety and adverse effects in patients with asthma. J Allergy Clin Immunol Pract 2018;6:776-81.
4. Ahn SH, Park SM, Park SY, Yoo JI, Jung HS, Nho JH, et al. Osteoporosis and osteoporotic fracture fact sheet in Korea. J Bone Metab 2020;27:281-90.
5. Dempster DW. Osteoporosis and the burden of osteoporosis-related fractures. Am J Manag Care 2011;17 Suppl 6:S164-9.
6. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res 2007;22:465-75.
7. Cloutier MM, Dixon AE, Krishnan JA, Lemanske RF Jr, Pace W, Schatz M. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program. JAMA 2020;324:2301-17.
8. Aljubran SA, Whelan GJ, Glaum MC, Lockey RF. Osteoporosis in the at-risk asthmatic. Allergy 2014;69:1429-39.
9. Dam TT, Harrison S, Fink HA, Ramsdell J, Barrett-Connor E; Osteoporotic Fractures in Men (MrOS) Research Group. Bone mineral density and fractures in older men with chronic obstructive pulmonary disease or asthma. Osteoporos Int 2010;21:1341-9.
10. Sasagawa M, Hasegawa T, Kazama JJ, Koya T, Sakagami T, Suzuki K, et al. Assessment of bone status in inhaled corticosteroid user asthmatic patients with an ultrasound measurement method. Allergol Int 2011;60:459-65.
11. Dahl R. Systemic side effects of inhaled corticosteroids in patients with asthma. Respir Med 2006;100:1307-17.
12. Kim S, Kim MS, You SH, Jung SY. Conducting and reporting a clinical research using Korean Healthcare Claims Database. Korean J Fam Med 2020;41:146-52.
13. Kong SH, Jo AJ, Park CM, Park KI, Yun JE, Kim JH. Chronic airway disease as a major risk factor for fractures in osteopenic women: nationwide cohort study. Front Endocrinol (Lausanne) 2023;14:1085252.
14. Kim JH, Moon H, Noh J, Lee J, Kim SG. Epidemiology and prognosis of pheochromocytoma/paraganglioma in Korea: a nationwide study based on the National Health Insurance Service. Endocrinol Metab (Seoul) 2020;35:157-64.
15. Kim HS, Shin DW, Lee WC, Kim YT, Cho B. National screening program for transitional ages in Korea: a new screening for strengthening primary prevention and follow-up care. J Korean Med Sci 2012;27 Suppl:S70-5.
16. Ministry of Health and Welfare of Korea. Enforcement decree of the framework act on health examinations [Internet]. Sejong: Introduction of Korean Law Information Center; 2019 [cited 2024 Jul 4]. Available from: https://www.law.go.kr/LSW/eng/engLsSc.do?menuId=2&section=lawNm&query=health+examination&x=0&y=0#liBgcolor0.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
18. Jeong HG, Kim DY, Kang DW, Kim BJ, Kim CK, Kim Y, et al. Physical activity frequency and the risk of stroke: a nationwide cohort study in Korea. J Am Heart Assoc 2017;6:e005671.
19. Wolbers M, Blanche P, Koller MT, Witteman JC, Gerds TA. Concordance for prognostic models with competing risks. Biostatistics 2014;15:526-39.
20. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34:3661-79.
21. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083-107.
22. Hanania NA, Chapman KR, Sturtridge WC, Szalai JP, Kesten S. Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. J Allergy Clin Immunol 1995;96(5 Pt 1):571-9.
23. Monadi M, Javadian Y, Cheraghi M, Heidari B, Amiri M. Impact of treatment with inhaled corticosteroids on bone mineral density of patients with asthma: related with age. Osteoporos Int 2015;26:2013-8.
24. Weatherall M, James K, Clay J, Perrin K, Masoli M, Wijesinghe M, et al. Dose-response relationship for risk of non-vertebral fracture with inhaled corticosteroids. Clin Exp Allergy 2008;38:1451-8.
25. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomized controlled trials and observational studies. Thorax 2011;66:699-708.
26. Peng S, Tan C, Du L, Niu Y, Liu X, Wang R. Effect of frac-

ture risk in inhaled corticosteroids in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. BMC Pulm Med 2023;23:304.
27. Komori T. Glucocorticoid signaling and bone biology. Horm Metab Res 2016;48:755-63.
28. Altonsy MO, Mostafa MM, Gerber AN, Newton R. Long-acting β2-agonists promote glucocorticoid-mediated repression of NF-κB by enhancing expression of the feedback regulator TNFAIP3. Am J Physiol Lung Cell Mol Physiol 2017;312:L358-70.
29. Haque R, Hakim A, Moodley T, Torrego A, Essilfie-Quaye S, Jazrawi E, et al. Inhaled long-acting β2 agonists enhance glucocorticoid receptor nuclear translocation and efficacy in sputum macrophages in COPD. J Allergy Clin Immunol 2013; 132:1166-73.
30. Kondo H, Togari A. Continuous treatment with a low-dose β-agonist reduces bone mass by increasing bone resorption without suppressing bone formation. Calcif Tissue Int 2011; 88:23-32.
31. Nuntapornsak A, Wongdee K, Thongbunchoo J, Krishnamra N, Charoenphandhu N. Changes in the mRNA expression of osteoblast-related genes in response to beta(3)-adrenergic agonist in UMR106 cells. Cell Biochem Funct 2010;28:45-51.
32. Polosa R. Critical appraisal of antileukotriene use in asthma management. Curr Opin Pulm Med 2007;13:24-30.
33. Cazzola M, Page CP, Matera MG, Rogliani P, Hanania NA. Revisiting asthma pharmacotherapy: where do we stand and where do we want to go? Eur Respir J 2023;62:2300700.
34. Al-Azzam N, Elsalem L. Leukotriene D4 role in allergic asthma pathogenesis from cellular and therapeutic perspectives. Life Sci 2020;260:118452.
35. Ren W, Dziak R. Effects of leukotrienes on osteoblastic cell proliferation. Calcif Tissue Int 1991;49:197-201.
36. Wixted JJ, Fanning PJ, Gaur T, O'Connell SL, Silva J, Mason-Savas A, et al. Enhanced fracture repair by leukotriene antagonism is characterized by increased chondrocyte proliferation and early bone formation: a novel role of the cysteinyl LT-1 receptor. J Cell Physiol 2009;221:31-9.