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Association of COX-2 Selectivity in Pain Medication Use with Endometriosis Incidence: Retrospective Cohort Study

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Purpose: This retrospective cohort study aimed to investigate the association between the use of pain medications with varying cyclooxygenase-2 (COX-2) selectivity and the incidence of endometriosis (EMS) in women.

Materials and Methods: Medical records from January 1, 1994, to December 31, 2022, were retrospectively analyzed. The cohort included 33406 patients diagnosed with any pain-related condition who were prescribed either selective COX-2 inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs). Patients were followed for up to 5 years from the cohort entry date. The incidence of EMS was compared between the two medication groups using Cox proportional hazards models, adjusting for confounding factors such as age, past drug use, and prior diagnosis.

Results: The incidence rates of EMS were 3.00 per 1000 person-years in the COX-2 inhibitor group and 3.97 per 1000 person-years in the NSAIDs group. After adjustment for confounders, the hazard ratio for EMS incidence in the COX-2 inhibitor group compared to the NSAIDs group was 0.77 [95% confidence interval (CI), 0.63 to 0.93; $p<0.01$], indicating a significantly lower risk in the COX-2 inhibitor group. Subgroup analysis revealed that this association was particularly significant in younger women aged 20–44 years, with a hazard ratio of 0.71 (95% CI, 0.54 to 0.95; $p<0.05$) in this age group.

Conclusion: The findings suggest that COX-2 inhibitors may reduce the incidence of EMS compared to traditional NSAIDs, highlighting their potential as a strategic option for managing EMS, particularly among younger women. Further prospective studies are needed to confirm these findings.

Key Words: Endometriosis, COX-2, OMOP-CDM, Celecoxib, Ibuprofen, Cohort Study

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INTRODUCTION

Endometriosis (EMS) affects 5%–15% of all women of reproductive age and 20%–50% of infertile women,[1] causing dysmenorrhea, dyspareunia, pelvic or lower abdominal pain, and infertility, leading to significantly decreased quality of life in reproductive women.[2] EMS is a chronic inflammatory condition characterized by the growth of endometrial tissue outside the uterus, primarily affecting the ovaries, fallopian tubes, and pelvic peritoneum.[3] It can be characterized by the accumulation of various pro-inflammatory cytokines and chemokines, such as interleukin-1β and tumor necrosis factor-α.[1] Molecules activate nuclear factor κB and hypoxia-inducible factor-1α signaling pathways, resulting in elevated COX-2 expression.[4] These

substances within the pelvic cavity and endometrial tissues play crucial roles in inflammation, adhesion formation, and neovascularization, significantly contributing to the progression of the disease.[5]

Hormonal therapies, including progestins, dienogest, and GnRH-agonists, are known to be effective in alleviating symptoms of EMS. However, their mechanism of action may inhibit ovulation and diminish fertility, making them inappropriate for patients who are attempting to conceive.[6] Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used as a first-line treatment for women with EMS-related pain due to their relatively few side effects and over-the-counter availability.[7] NSAIDs primarily focus on symptom or pain relief, and some studies suggest they may not be consistently effective even for managing pain. For example, clinical trials with typical NSAIDs (e.g., naproxen) failed to provide evidence of a positive effect on pain compared to a placebo control.[7] Furthermore, a 2018 review on pharmacological treatments for EMS concluded that NSAIDs, while effective in managing pain, do not address the underlying disease pathology.[8] Similarly, a recent scoping review on treatments for EMS-related pelvic pain emphasized that although NSAIDs are widely used, they lack robust evidence for efficacy and do not address the root causes of the disease.[9]

NSAIDs inhibit the COX enzyme, responsible for producing prostaglandin, an inflammatory substance, by reducing arachidonic acid generated from the breakdown of membrane phospholipids.[10] Two isoforms exist: COX-1, predominantly found in the gastrointestinal tract, and COX-2, an inducible enzyme that increases expression during inflammation.[11] Selective COX-2 inhibitors inhibit COX-1 less and COX-2 more selectively, showing potential as effective anti-inflammatory drug therapies.[12]

In patients with EMS, COX-2 expression is elevated significantly in the endometrial glandular epithelium, endometrial stroma,[13] and ovarian endometriotic tissue during the secretory phase compared with control groups.[14] Additionally, ectopic lesions highly express COX-2 in EMS patients experiencing chronic stress.[15] Clinical studies have shown that overexpression of aromatase upregulates COX-2, promoting prostaglandin E2 production, creating a positive feedback loop, suggesting that COX-2 inhibitors may be an option for analgesic control in EMS.[16]

Despite their theoretical advantages, the impact of selective COX-2 inhibitors on EMS incidence remains unexplored. Understanding their influence on EMS incidence is crucial as it provides insights into whether these drugs could not only relieve symptoms but also reduce the likelihood of EMS development or recurrence. Assessing incidence allows us to evaluate long-term therapeutic effects beyond symptomatic relief.

To address this gap, we conducted a large retrospective cohort study comparing the incidence rates of EMS in patients prescribed selective COX-2 inhibitors versus traditional NSAIDs. By analyzing data from 15 observational Korean databases, this study aimed to clarify whether selective COX-2 inhibitors can serve as a dual-purpose treatment for EMS, targeting both symptoms and disease incidence.

MATERIALS AND METHODS

Data sources

This study included patient-based retrospective cohort data from 15 medical centers that have converted to the Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM) standard in South Korea. The Observational Health Data Sciences and Informatics (OHDSI) organization provides open-source solutions to use large-scale observational health data for various clinical research,[17] and OHDSI's OMOP-CDM has been adopted for pharmacoepidemiologic and pharmacovigilance studies.[18] The OMOP-CDM is vital for generating network-wide results in the Distributed Research Network by allowing consistent analysis across collaborating organizations.[18] These data contain longitudinal, real-world patient data from electronic health records, claims, and registries, providing a diverse and representative sample of patients. We accessed the database through the ATLAS platform and analyzed the electronic medical records (EMR) data of each hospital converted to OMOP-CDM. The patient data we analyzed spanned from January 1, 1994, to December 31, 2022. The data was accessed for the period from January 30, 2023, to December 22, 2023. This study was approved by the Institutional Review Board at our institution (AJOUIRB-DB-2023-046) and exempt from IRBs at other institutions due to the Research Free Zone agreement.

Study design

We conducted a retrospective, observational, comparative cohort study to observe the incidence of EMS in patients using selective COX-2 inhibitors compared to those using traditional NSAIDs. OMOP-CDM was used to extract and analyze patient data from databases of 15 different medical centers in South Korea. Consequently, we compared the incidence rates of patients prescribed COX-2 inhibitors to those prescribed traditional NSAIDs across each of the 15 medical centers and for all patients (Fig. 1). We obtained the hazard ratio (HR) through a COX proportional hazard model and presented the cumulative incidence rate plot from Kaplan–Meier fitting. Additionally, we derived the risk ratio for all patients through meta-analysis.

Study population and cohort structure

The study population was divided into a target cohort and a comparator cohort (Fig. 2). The target cohort included adult women aged 20 to 59 years who were new selective COX-2 inhibitors users. The comparator cohort included adult women aged 20 to 59 years who were new traditional NSAIDs users.

Cohort entry date was defined as the first date in the pa-

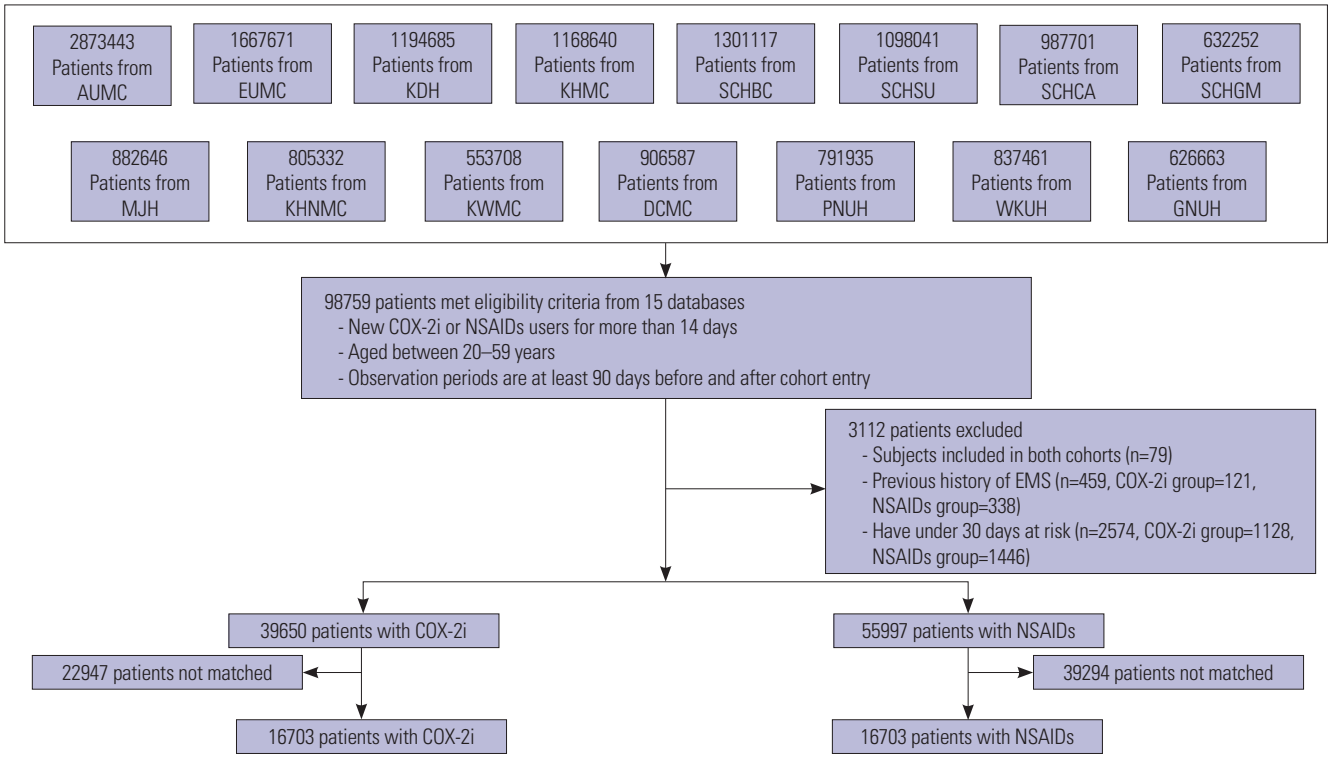

Fig. 1. Study flowchart of included patient-based retrospective cohort data collected from 15 medical centers across South Korea. COX-2i, selective COX-2 inhibitors; NSAIDs, traditional NSAIDs; EMS, endometriosis; NSAIDs, nonsteroidal anti-inflammatory drugs.

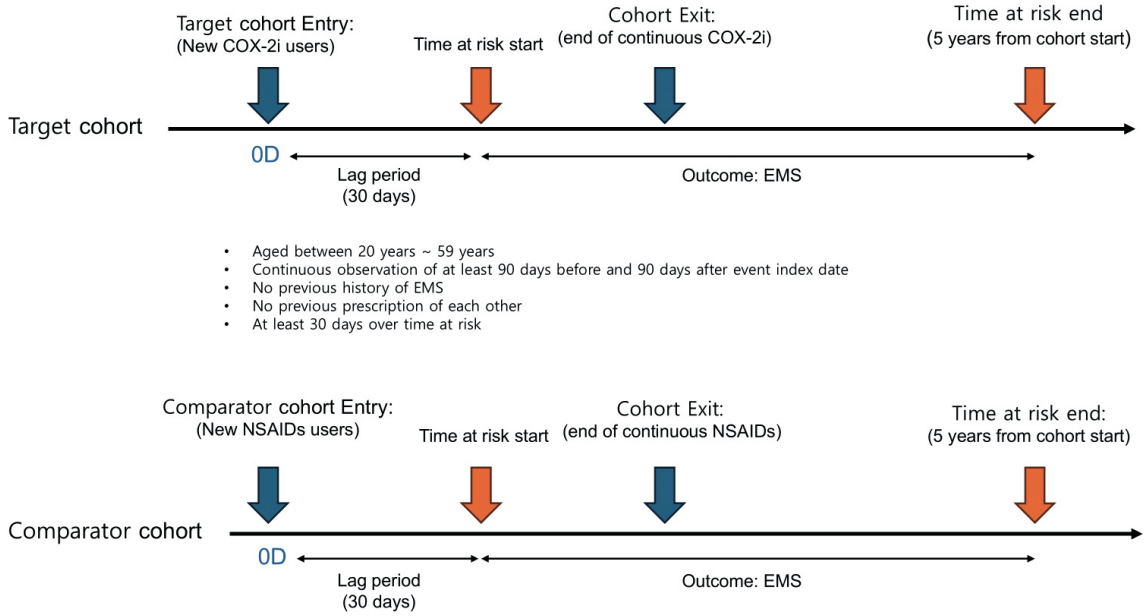

Fig. 2. Diagram of cohort construction showing target (COX-2i) and comparator (NSAIDs) groups. COX-2i, selective COX-2 inhibitors; NSAIDs, traditional NSAIDs; EMS, endometriosis; NSAIDs, nonsteroidal anti-inflammatory drugs.

tient's history when they started taking the selective COX-2 inhibitors or traditional NSAIDs for at least 14 days. In this investigation, which was designed as a longitudinal study with a duration of up to 5 years, we focused on acquiring data relevant to long-term drug users. It was noted that NSAID prescriptions lasting 10 days or less are typically considered short-term use.[19] Consequently, individuals characterized by short-term usage were systematically excluded. For the purposes of this study, long-term usage was delineated as the administration of selective COX-2 inhibitors or traditional NSAIDs exceeding a period of 14 days.

Cohort exit was defined as the end of continued prescription.

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The time-at-risk (TAR) to observe the occurrence of an outcome was set to 30 days after cohort entry and 5 years after cohort exit. The delineation of the TAR commencing 30 days after cohort entry was deliberately chosen to account for the temporal dynamics between drug administration and the onset of measurable clinical outcomes. This interval serves to mitigate the confounding effect of immediate diagnoses coinciding with the initiation of medication use, thereby ensuring that any observed outcomes can more reliably be attributed to the drug's influence.

Patients were excluded from the cohorts if they met any of the following criteria: diagnosis of EMS before cohort entry, inclusion in both the target and comparator cohorts, and having at least 90 days of observation before cohort entry and after cohort exit. The 90-day observation period before cohort entry ensures fair collection and control of covariates and patient information, setting a standardized baseline for all participants. After cohort exit, the subsequent 90-day window addresses the risk of patients being censored due to discontinued hospital visits, maintaining the integrity of our longitudinal analysis.

Informed consent from individual patients was waived as all registries were curated in a de-identified form. This study was conducted in accordance with the Declaration of Helsinki, and the results were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline. The datasets generated during and/or analyzed in the current study are not publicly available, but are available from the corresponding author upon reasonable request.

Identify of target and comparative drug use

The exposure of interest was the initiation of treatment with either a selective COX-2 inhibitor or a traditional NSAID for at least 14 days. Selective COX-2 inhibitors was defined as celecoxib, nimesulide, meloxicam, etodolac, and diclofenac, which are five highly selective and commonly used NSAIDs that have been observed to have high COX-2 inhibition selectivity in previous studies.[20] In contrast, traditional NSAIDs was defined as naproxen, piroxicam, nabumetone, ketoroloac, ibuprofen, indomethacin, and sulindac, which are seven commonly used NSAIDs that have been observed in previous studies to have either no selectivity for COX-1, 2 inhibition or relatively high selectivity for COX-1 inhibition.[20] Patients were categorized into the target and comparator cohorts based on the medications they were prescribed.

Outcome measures

The primary outcome measure focused on the first incidence of EMS in a patient's history during the at-risk period. In our retrospective analysis of EMR from each participating hospital, the primary outcome—incidence of EMS—was determined based on clinical diagnoses made by healthcare professionals across these institutions. Events were recorded when physicians diagnosed patients with EMS, leveraging a combination of clinical examination findings and, where applicable, imaging studies. EMS has been reported to involve a significant delay between symptom onset and diagnosis, with studies indicating a diagnostic delay of 6.7 years in women aged 18–45 years.[21] Therefore, a long follow-up time should be established. Considering the limitations in controlling confounding variables after cohort entry, we ultimately set a follow-up time of 5 years.

Statistical analysis

In this study, we utilized ATLAS version 2.7.6 and conducted our analysis on the FEEDERNET platform, a health big-data platform based on the OMOP-CDM and supported by a Korean national project. On the ATLAS platform, EMR data from each medical centers are anonymized, standardized, and stored in OMOP-CDM format, and the same statistical analysis can be performed on these datasets across multiple institutions. We used the ATLAS platform to collect cohort data of patients prescribed COX-2 inhibitors and traditional NSAIDs according to predefined criteria, and to monitor the occurrence of EMS events within the cohort for analysis. We used multivariable regression models with propensity score adjustments for potential confounders, including age, prior drug use, prior disease, time in cohort, index year, and Charlson's comorbidity index measured 30 and 365 days before the cohort entry date. To succinctly illustrate EMS incidence over time across cohorts, we opted for cumulative event rate plots instead of traditional Kaplan–Meier plots. These are calculated as the complement of the survival function (1-survival function), offering a direct and clear depiction of event progression. The Cox proportional hazards model was used to assess the statistical significance of the differences, and the HRs and *p*-values were plotted on the cumulative event rate graphs. Utilizing the "metafor" package in R software, we conducted a meta-analysis on EMS events across data from each 15 medical centers during the follow-up period. The low I^2 value of 0% observed in our heterogeneity analysis reflects the minimal variability among study outcomes, likely attributable to the uniform application of the OMOP-CDM framework in the design and analysis of each study included in this meta-analysis. Consequently, we employed a fixed effects model for the analysis to accommodate the observed variability across the included studies.

All analyses were performed using a two-sided significance level of 0.05. *p*-values are reported as exact values when significant (e.g., $p=0.0085$), while results are summarized using thresholds (e.g., $p<0.05$, $p<0.01$) for consistency and readability. Statistical analyses were conducted using Python software, version 3.10.10 and R software, version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity analysis

To assess the robustness of the results, several sets of sensitivity analyses were performed using subgroup analysis, different definitions of TAR, and stratification. First, different TAR peri-

ods (1 or 3 years) were applied. Second, subgroup analyses were performed in two ways: first, we divided the groups by age into two group intervals to analyze the risk ratios, and second, we limited the risk ratios to celecoxib, known for its relatively high COX-2 selectivity, and ibuprofen, known for its relatively high COX-1 selectivity, among COX-2 inhibitors. To ensure control of confounding variables and clear visibility of survival analysis outcomes in the subgroup analysis as well, we utilized 1:1 propensity score matching.

Data interpolation

In OMOP-CDM, each patient's data is anonymized and only the statistical analysis of all data from each medical center is available. Although survival analysis and HRs can be obtained from each database, a survival analysis that includes all individual patient data simultaneously is not possible. Therefore, to aggregate the results of all 15 medical centers, we employed an interpolation method that estimated the time-specific survival functions by synthesizing survival analysis results from each database. This approach allowed us to approximate the cumulative survival function for the entire cohort, reconstructing sufficient raw data to perform Cox proportional hazards survival analysis across all 33706 patients. This allowed us to estimate and approximate the time-specific survival function for all patients, and then recreate the raw data for all 33706 patients needed to obtain this survival function for the Cox proportional hazard model survival analysis. Consequently, survival analysis and HRs were estimated for the entire medical center data. Data interpolation was conducted using Python software, version 3.10.10.

RESULTS

Study population and baseline characteristics

In this study, 98759 patients aged 20 to 59 years with a prescrip-

Table 1. Baseline Characteristics of the Target and Comparator Cohorts Before and After Propensity Score Matching

Characteristics	Before PS matching			After PS matching		
	COX-2i (%)	NSAIDs (%)	SMD	COX-2i (%)	NSAIDs (%)	SMD
Age group (yr)						
20–24	2.7	5.8	-0.15	3.5	3.2	0.02
25–29	4.5	7.0	-0.11	6.3	6.1	0.01
30–34	7.4	8.1	-0.02	7.6	7.8	0
35–39	10.4	11.2	-0.02	10.8	10.5	0.01
40–44	14.1	13.6	0.01	12.7	13.6	-0.03
45–49	17.2	16.8	0.01	17.3	16.3	0.02
50–54	22.9	18.7	0.10	20.8	21.0	0
55–59	20.8	18.8	0.05	21.0	21.6	-0.01
Medical history						
Diabetes mellitus	1.9	3.8	-0.11	2.6	2.7	0
Gastroesophageal reflux disease	5.0	2.7	0.12	3.4	3.4	0
Hypertensive disorder	4.0	7.6	-0.16	5.0	4.6	0.02
Malignant neoplastic disease	2.4	21.1	-0.61	4.6	4.4	0.01
Malignant tumor of breast	0.9	10.6	-0.43	1.9	1.9	0
Medication use						
Antibacterials for systemic use	22.9	52.8	-0.65	29.0	27.4	0.04
Antidepressants	10.6	16.1	-0.16	15.1	14.5	0.02
Antiinflammatory and antirheumatic products	8.3	0.7	0.37	2.2	2.2	0.01
Antineoplastic agents	11.9	13.3	-0.04	5.8	6.2	-0.02
Antithrombotic agents	6.5	12.6	-0.21	8.2	7.6	0.02
Beta blocking agents	2.7	8.4	-0.25	3.8	3.3	0.03
Calcium channel blockers	4.6	9.5	-0.19	5.8	4.9	0.04
Diuretics	4.7	11.1	-0.24	6.7	5.9	0.03
Drugs for obstructive airway diseases	11.6	34.1	-0.56	12.7	11.2	0.05
Drugs used in diabetes	2.3	5.4	-0.16	3.4	3.0	0.02
Immunosuppressants	13.3	2.9	0.39	5.7	6.2	-0.02
Opioids	23.8	39.1	-0.33	24.2	23.0	0.03

COX-2i, selective COX-2 inhibitors; NSAIDs, traditional NSAIDs; PS, propensity score; SMD, standardized mean difference; NSAIDs, nonsteroidal anti-inflammatory drugs.

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Table 2. Incidence Rates and Risk of EMS between Selective COX-2i Users and Traditional NSAIDs Users

Database	Number of subjects		Mean follow-up time (days)		Number of outcome (EMS) events		Incidence rate per 1000 patient-years		Relative rate
	COX-2i	NSAIDs	COX-2i	NSAIDs	COX-2i	NSAIDs	COX-2i	NSAIDs	
AUMC	3522	3522	1333	1326	33	47	2.57	3.67	0.70
KHMC	2076	2076	1312	1278	31	39	4.15	5.36	0.77
DCMC	1834	1834	1343	1357	9	12	1.33	1.76	0.76
EUMC	1383	1383	1298	1329	17	21	3.46	4.17	0.83
SCHBC	1324	1324	1213	1193	18	37	4.09	8.55	0.48
WKUH	949	949	1470	1474	6	11	1.57	2.87	0.55
KHNMC	895	895	1275	1222	10	16	3.20	5.34	0.60
SCHCA	890	890	1156	1153	18	20	6.38	7.11	0.90
SCHSU	730	730	1147	1197	14	11	6.10	4.59	1.33
MJH	640	640	1230	1325	2	2	0.93	0.86	1.08
GNUH	621	621	1026	1023	3	2	1.72	1.15	1.50
PNUH	620	620	1073	1112	8	5	4.39	2.65	1.66
KDH	557	557	1374	1363	3	5	1.43	2.40	0.60
KWMC	452	452	1288	1317	2	3	1.25	1.84	0.68
SCHGM	210	210	1225	1268	2	2	2.84	2.74	1.04
Total	16703	16703	1280	1282	176	233	3.00	3.97	0.76

EMS, endometriosis; COX-2i, selective COX-2 inhibitors; NSAIDs, traditional NSAIDs; NSAIDs, nonsteroidal anti-inflammatory drugs.
Data were collected from 15 medical centers across South Korea.

tion for either selective COX-2 inhibitors or traditional NSAIDs for over 14 days were identified from 15 cohorts. The inclusion criteria required an observation period of at least 90 days before and after the prescription start date. Out of the total patients, 3112 were excluded: 79 subjects were present in both cohorts, 459 had a history of EMS, and 2574 had a TAR of less than 30 days. Following propensity score matching, the matched cohort comprised 33406 participants, with 16703 in the selective COX-2 inhibitors cohort and 16703 in the traditional NSAIDs cohort. Fig. 1 shows the participant selection process.

Table 1 shows the participants' baseline characteristics before and after propensity score matching. After matching, the two cohorts of new users were comparable for all observed features, with no standardized mean difference exceeding 0.1.

Association of drug dispensation with EMS

Table 2 shows the incidence rate of EMS in the selective COX-2 inhibitors group and the traditional NSAIDs group {5-year cumulative incidence of EMS, 3.00 [95% confidence interval (CI), 2.59 to 3.39] per 1000 patient-years in the selective COX-2 inhibitors cohort verses 3.97 (95% CI 3.49 to 4.43) per 1000 patient-years in the traditional NSAIDs cohort}.

We conducted survival analysis for the incidence of EMS between selective COX-2 inhibitors and traditional NSAIDs. Fig. 3 shows a cumulative incidence plots from Kaplan–Meier fitting of the entire cohort re-estimated from the anonymized survival functions of the 15 individual medical centers (Fig. 3). During 5 years of follow-up, participants with a prescription of selective COX-2 inhibitors had a significantly lower risk (RR) of EMS [HR, 0.77 (95% CI, 0.63 to 0.93); p=0.0085].

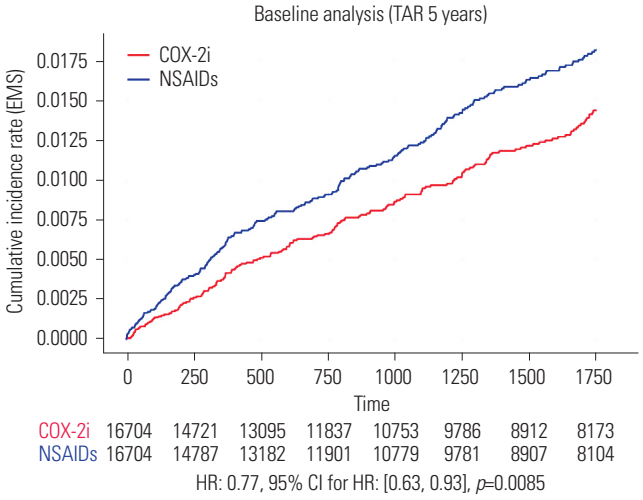

Fig. 3. Cumulative incidence plots from Kaplan–Meier fitting for EMS outcomes over 5 years, comparing COX-2i and NSAIDs users before and after propensity score matching. TAR, time-at-risk; COX-2i, selective COX-2 inhibitors; NSAIDs, traditional NSAIDs; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; CI, confidence interval.

In the distributed network analysis with 1:1 propensity score matching, the selective COX-2 inhibitors users demonstrated a significantly RR [0.76 (95% CI, 0.62 to 0.92)] compared to the traditional NSAIDs users (Fig. 4). In particular, the top eight databases, which encompassed a large number of observed patients, consistently demonstrated a risk ratio of less than 1.

Subgroup analyses

In age-stratified subgroup analyses, the COX-2 inhibitor group showed a significantly lower EMS risk in younger patients

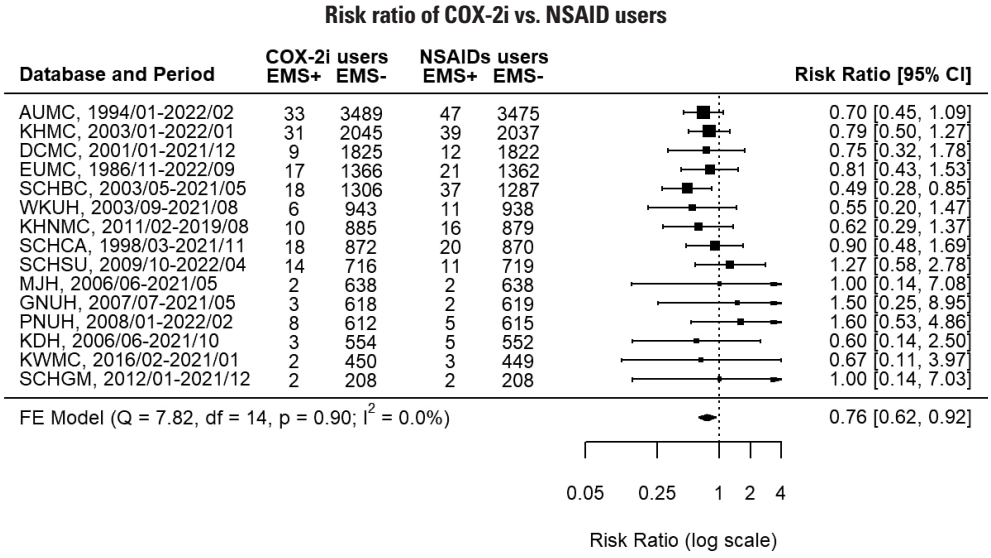

Fig. 4. Forest plot from meta-analysis comparing the incidence of EMS between COX-2i and NSAIDs users across 15 medical centers. COX-2i, selective COX-2 inhibitors; NSAIDs, traditional NSAIDs; EMS+, patients diagnosed with EMS during follow-up; EMS-, patients without EMS diagnosis during follow-up; NSAIDs, nonsteroidal anti-inflammatory drugs; CI, confidence interval; EMS, endometriosis.

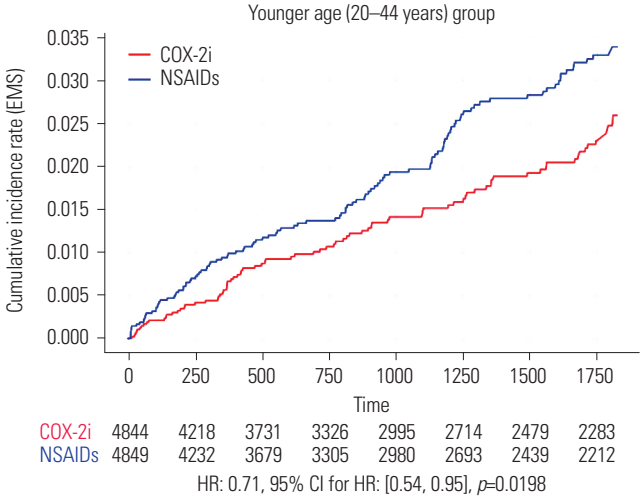

Fig. 5. Subgroup analysis of EMS risk for younger patients (20–44 years). The COX-2 inhibitor group showed a significantly lower EMS risk compared to the NSAIDs group [HR, 0.71 (95% CI, 0.54–0.95); p<0.0198]. COX-2i, selective COX-2 inhibitors; NSAIDs, traditional NSAIDs; EMS, endometriosis; NSAIDs, nonsteroidal anti-inflammatory drugs; CI, confidence interval; HR, hazard ratio.

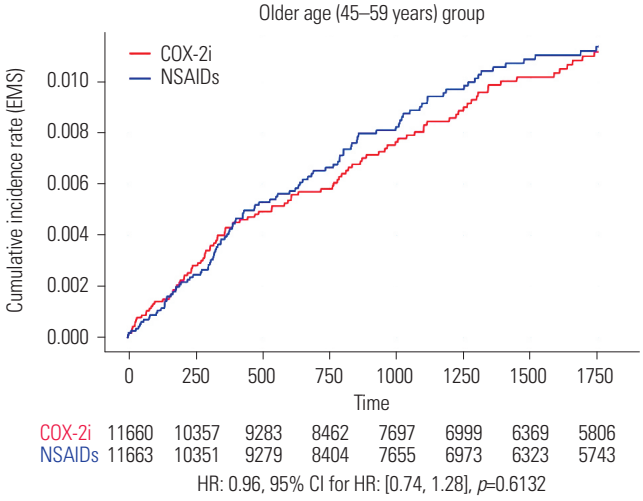

Fig. 6. Subgroup analysis of EMS risk for older patients (45–59 years). No significant difference in EMS risk was observed between the COX-2 inhibitor and NSAIDs groups [HR, 0.96 (95% CI, 0.74–1.28); p=0.6132]. COX-2i, selective COX-2 inhibitors; NSAIDs, traditional NSAIDs; EMS, endometriosis; NSAIDs, nonsteroidal anti-inflammatory drugs; CI, confidence interval; HR, hazard ratio.

aged 20–44 years [HR, 0.71 (95% CI, 0.54 to 0.95); p=0.0198] (Fig. 5). However, no significant difference in EMS risk was observed in the older group aged 45–59 years [HR, 0.96 (95% CI, 0.74 to 1.28); p=0.6132] (Fig. 6).

Additionally, a subgroup analysis comparing celecoxib (high COX-2 selectivity) and ibuprofen (high COX-1 selectivity) showed a lower incidence of EMS in the celecoxib group [RR= 0.81 (95% CI, 0.63 to 1.07); p=0.1463], though the difference was not statistically significant (Supplementary Fig. 1, only online).

Sensitivity analyses

To assess the robustness of the findings, sensitivity analyses were conducted by varying the TAR period. The results demonstrated a significantly lower EMS risk in the COX-2 inhibitor group for both the 3-year [HR, 0.77 (95% CI, 0.61 to 0.98); p=0.0374] (Supplementary Fig. 2, only online) and 1-year TAR conditions [HR, 0.69 (95% CI, 0.50 to 0.96); p=0.0259] (Supplementary Fig. 3, only online). Detailed sensitivity analyses with varying TAR periods and additional subgroup comparisons are presented in Supplementary Figs. 1–3 (only online) for further context.

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DISCUSSION

Our study, conducted across multiple medical centers in South Korea, demonstrates that patients prescribed COX-2 inhibitors experienced a reduced incidence of EMS over 5 years compared to those administered non-selective COX inhibitors. This finding aligns with prior research suggesting a therapeutic role for COX-2 inhibitors in EMS management and provides new insights from a large-scale, retrospective evaluation of real-world data. The observed differential impact among younger patients suggests a potential age-dependent effect, emphasizing the need for further investigation into this relationship.

While our findings suggest a promising potential of COX-2 inhibitors in both symptomatic relief and possibly in influencing the course of EMS, clinicians should exercise caution before considering them as a primary management tool. COX-2 inhibitors suppress prostaglandin E2 (PGE2), a key mediator upregulated in EMS lesions,[22] and may indirectly reduce estrogen levels through aromatase inhibition. These pathways underscore their dual potential in symptom control and disease progression modification. Based on the mechanisms of COX-2 inhibitors, their potential in managing EMS extends beyond symptom relief to modifying disease progression. COX-2 plays a critical role in synthesizing PGE2, which is significantly upregulated in endometriotic lesions and contributes to inflammation and pain.[23] By inhibiting COX-2, PGE2 production is reduced, thereby alleviating inflammation and pain associated with EMS. Additionally, PGE2 stimulates the expression of aromatase, an enzyme that facilitates local estrogen synthesis.[23] Suppressing PGE2 through COX-2 inhibition may downregulate aromatase activity, subsequently lowering estrogen levels and potentially inhibiting lesion growth.[15] These mechanisms highlight the dual potential of COX-2 inhibitors in both symptom management and disease modulation.

A major strength of our study is its large sample size, which bolsters the reliability of our conclusions. Additionally, the use of real-world data from multiple centers enhances the study's generalizability within the South Korean population. However, the prolonged developmental phase of EMS presents challenges for accurate identification through electronic health records, as reflected in the relatively small number of outcomes compared to the total sample size. Moreover, the demographic and clinical characteristics unique to South Korea may limit the applicability of our findings to other populations.

One potential limitation of this study is the risk of bias introduced by censoring and unmeasured confounding variables. Patients lost to follow-up or those who discontinued their prescribed medication during the observation period may have influenced the estimation of EMS incidence. While we mitigated this risk by excluding patients with less than 90 days of follow-up and using a 30-day grace period for medication discontinuation, residual bias cannot be entirely ruled out. Additionally, as this study was conducted retrospectively using EMR data, certain confounding variables such as body mass index, dietary habits, and physical activity—known to potentially influence EMS risk—were not included in the analysis. Such censoring and unmeasured confounders could have disproportionately affected the results if patients at higher risk of EMS were more likely to discontinue treatment, leave the study cohort, or exhibit behaviors or characteristics not captured in the dataset. Future studies with more robust tracking of follow-up data and inclusion of additional variables, as well as alternative analytical methods such as multiple imputation for missing data, may address these limitations.

In conclusion, our findings have potential implications for clinical practice, particularly in guiding pain management strategies for EMS patients. Given the observed reduction in EMS incidence with COX-2 inhibitors, these agents may offer a dual benefit of symptom relief and reduced disease progression risk. However, while our results are promising, COX-2 inhibitors should not yet be considered a first-line treatment option due to the need for further evidence from prospective, randomized trials. Current prescribing habits may prioritize these inhibitors for patients who do not respond adequately to traditional NSAIDs or hormonal therapies. Incorporating COX-2 inhibitors into clinical guidelines will require additional research to confirm their long-term safety, efficacy, and cost-effectiveness. Until then, clinicians should evaluate the use of COX-2 inhibitors on a case-by-case basis, considering individual patient needs and risk profiles.

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AUTHOR CONTRIBUTIONS

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