Retrospective Study

Epidural Steroid Injections and the Risk of Osteoporosis in Lumbar Spondylosis Patients: A Nationwide Population-Based Cohort Study

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Background: Epidural steroid injections (ESIs) involve the administration of steroids and local anesthetics into the spinal epidural space, and they are performed by inserting a needle between the ligamentum flavum and dura. This procedure is suitable for patients with lumbosacral radiculopathy secondary to disc herniation or postsurgical radicular pain. The relief period of the analgesic medications may be prolonged by > 6 weeks, resulting in nonsurgical management becoming a suitable option. However, the negative effect of ESIs on bone mineral density has been reported.

Objectives: We aimed to clarify the association between ESIs and osteoporosis risk by analyzing a nationwide population database.

Study Design: This study is a nationwide retrospective cohort study.

Setting: Data on 1 million cases randomly selected from the 2000 Registry for Beneficiaries of the National Health Insurance Research Database (NHIRD) were collected.

Methods: In total, 4,957 patients who were diagnosed with lumbar spondylosis and received ESIs between 2000 and 2013 were identified from the NHIRD. Subsequently, another 4,957 patients with lumbar spondylosis were randomly selected from the same database and frequency matched by age, gender, and index year with the patients who received ESIs.

Results: The mean age of the patients were 50.3 ± 17.1 years. The incident rates of osteoporosis in the ESI and non-ESI groups were 7.95 and 7.01 per 1,000 person-years, respectively. Osteoporosis risk was significantly higher in the ESI cohort than in the non-ESI cohort (absolute standardized hazard ratio = 1.23, 95% confidence interval = 1.05-1.45, P = 0.01). The risk factors for osteoporosis were old age, being female, and undergoing ESIs. Osteoporosis risk was significantly higher in the ESI cohort than in the non-ESI cohort in the male, lowest-urbanization-level (fourth level), other-occupations, and comorbidity-free subgroups.

Limitations: The NHIRD did not provide information on osteoporosis-related scales, renal function, blood pressure, smoking habit, pulmonary function, daily activities, and dosage of injected steroids.

Conclusions: For patients diagnosed with lumbar spondylosis, ESIs are associated with a high osteoporosis risk. Thus, this therapy should be recommended with caution, especially for patients with correlated risk factors (e.g., high risk of osteoporotic fracture, low socioeconomic status, and retired or unemployed status).

Key words: Lumbar spondylosis, epidural steroid injection, osteoporosis, urbanization level

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Lumbar spinal stenosis causes substantial pain and disability, and it is the most common reason for spinal surgery among patients aged older than 65 years (1). Prior to surgical treatment, nonsurgical management options that are available include lifestyle modification, medication use, physiotherapy, and spinal injections (2). Epidural injection is a spinal procedure that involves the injection of isolated local anesthetic solutions, steroids, or both into the spinal epidural space to relieve pain, improve function and mobility, and prolong healing time (3). Epidural spinal injections (ESIs) were first administered by Sicard in 1901 for lumbago, and such injections were limited to local anesthesia during the first 50 years of its use. In the early 1950s, steroids were added for pain relief in accordance with the recommendations of Robecchi and Capra and Lievre et al (4,5). Gradually, this novel spinal procedure became an accepted method for managing low back pain, lower extremity pain, and radiculopathy secondary to intervertebral disc herniation or other degenerative spinal pathologies (6).

Lewis et al (7,8) conducted a systematic review and developed an economic model to investigate the clinical effectiveness and cost-effectiveness of management strategies for sciatica. The results of this model indicate the effectiveness of epidural corticosteroid injections and disc surgery. In another systematic review (8), network meta-analyses of 122 relevant studies and 21 treatment strategies were conducted to compare the clinical effectiveness of various management strategies for sciatica, and its results revealed statistically significant improvements. Furthermore, the aforementioned network meta-analyses revealed that ESIs are superior to traction, percutaneous discectomy, and exercise therapy for treating sciatica (8). Additionally, radicular nerve pain and its associated symptoms can be attributed to the inflammatory status mediated by neurochemical mediators, which include phospholipase A2 and neuropeptides (e.g., substance P, vasoactive intestinal peptide, and calcitonin gene-related peptide) that may be released by an injured nucleus. An increase in the local concentrations of these neuropeptides is believed to sensitize free nerve endings, resulting in painful discharges and back pain. The exact mechanism of action of the injected drugs remains unclear, although it is probably multivariate and involves anti-inflammatory effects, neural membrane stabilization effects, and the modulation of peripheral nociceptor inputs (3).

However, several studies (9,10) have reported the negative effects of ESIs on bone mineral density (BMD). A multicenter randomized control trial (9) reported the risk of cortisol suppression at 3 weeks among patients who received epidural corticosteroid injections, particularly those involving the use of longer-acting insoluble corticosteroid formulations. In a retrospective review, Nah et al (10) revealed that glucocorticoids can cause a host of adverse effects. The administration of exogenous glucocorticoids can reduce BMD and increase fracture risk. Most complications of oral, intramuscular, and intravenous steroid administration have been extensively reported. However, the causal relationship between ESIs and BMD reduction requires further clarification (11). Because of the increasing demand for effective symptom relief as a form of conservative management prior to surgery, a comprehensive study must be conducted to examine the effects of ESIs. Thus, the present study aimed to clarify the association between ESIs and osteoporosis risk by examining a nationwide population database.

Methods

In the present study, data were retrieved from the Longitudinal Health Insurance Database 2000 (LHID2000). The LHID2000 contains the detailed health care data of one million beneficiaries for the years 1996 to 2011. These one million beneficiaries were randomly selected from the 23.8 million National Health Insurance (NHI) beneficiaries registered in the 2000 Registry for Beneficiaries of the National Health Insurance Research Database (NHIRD). Taiwan's NHI provides insurance coverage to more than 99% of the Taiwanese population, and 97% of the hospitals and clinics in Taiwan participate in the NHI program; consequently, the NHIRD contains extensive health and medical treatment data pertaining to insured individuals, such as outpatients, inpatients, and individuals, who took medications, underwent surgical treatments, or received other forms of medical care. The identity of each patient was anonymized with an encrypted identification number prior to the release of the data for research. The age and gender distributions of the sampled population were matched with those of the original database population. The diagnostic codes used in the present study were based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The personal information of patients in the NHIRD was encrypted to protect their privacy, and the researchers were provided with anonymous identification numbers associated with relevant claims information, which

comprised gender, date of birth, medical services received, and prescriptions. Therefore, patient consent was not required for access to the NHIRD. Because the present study fulfilled the conditions for exemption from the requirement of patient consent, this requirement was waived by the Institutional Review Board of China Medical University (CMUH104-REC2-115-CR2). Through the LHID2000 patient data for the years from 2000 to 2010, we enrolled patients aged > 20 years who had been diagnosed with lumbar spondylosis (ICD-9-CM codes 720-724). The index date was defined as the date of lumbar spondylosis diagnosis. Patients were excluded if they had preexisting osteoporosis (ICD-9-CM code 733.0), had received ESIs before the index date, or had incomplete information with respect to gender or age. The patients who had received at least one ESI after the index date were included in the ESI cohort. To form the control cohort (i.e., non-ESI group), we selected the patients who had not received any ESI after the index date from the same database and performed a greedy algorithm-based rematch. Propensity scores were calculated through logistic regression to estimate the probability of disease status on the basis of baseline variables, which comprised age, gender, and the comorbidities of cirrhosis (ICD-9-CM code 571), hypertension (ICD-9-CM codes 401-405), diabetes mellitus (ICD-9-CM code 250), chronic kidney disease (ICD-9-CM code 585), coronary artery disease (ICD-9-CM codes 410-414), chronic obstructive pulmonary disease (COPD; ICD-9-CM codes 490-492, 494, and 496), anxiety (ICD-9-CM code 300.0), depression (ICD-9-CM codes 296.2, 296.3, 300.4, and 311), epilepsy (ICD-9-CM code 345), cerebrovascular disease (ICD-9-CM codes 430-438), cancer (ICD-9-CM codes 140-209), rheumatoid arthritis (ICD-9-CM code 714.0), and systemic lupus erythematosus (ICD-9-CM code 710.0). All enrolled study patients were followed up until the diagnosis of osteoporosis (ICD-9-CM code 733.0), withdrawal from the NHI program, or the end of 2013, whichever was earlier. We also considered all-cause mortality and incorporated the Fine and Gray method (20) in our competing risk analysis.

The baseline characteristics of the ESI and non-ESI cohorts were compared by examining their standardized mean differences. A standardized mean difference of ≤ 0.1 indicated that the difference between the 2 cohorts was negligible. The incidence density rates (per 1,000 person-years [PY]) of osteoporosis, which were stratified by gender, age, and comorbidity, were calculated for both cohorts. We considered deaths (all-cause mortality) as a competing event in the analysis of osteoporosis risk. After the competing risk of death was analyzed using the Fine and Gray method (20), subhazard ratios and 95% confidence intervals (CIs) were calculated to estimate osteoporosis risk. If a patient had osteoporosis, which was a study outcome in the present study, the follow-up of the patient was discontinued. Thus, whether a patient had fatal or nonfatal osteoporosis did not affect this model. We also considered the competing risks of the patients without osteoporosis. Thus, the model was suitable for the present study. The variables in the multivariable model comprised age, gender, monthly income, and the comorbidities of cirrhosis, hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease, COPD, anxiety, depression, epilepsy, and cerebrovascular disease; all these variables were significantly different in the univariate Cox model. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC). The level of significance was set at 0.05, and 2-tailed tests were conducted (Table 1).

Results

The present study examined the data of 4,957 patients with lumbar spondylosis who received ESIs and 4,957 one-to-one frequency-matched patients with lumbar spondylosis who did not receive non-ESIs. The baseline characteristics of the matched cohorts were similar. The mean ages for the ESI and non-ESI cohorts were 50.2 ± 17.3 and 50.6 ± 16.7 years, respectively, and 59.5% of the patients were men (Table 1). The major comorbidities (Table 1) in both cohorts were hypertension (ESI vs non-ESI cohort, 29.5% vs 29.2%), liver cirrhosis (ESI cohort vs non-ESI cohort, 24.4% vs 23.6%), COPD (ESI cohort vs non-ESI cohort, 19.3% vs 18.5%), coronary artery disease (ESI cohort vs non-ESI cohort, 16.2% vs 15.3%), anxiety (ESI cohort vs non-ESI cohort, 13.2% vs 12.4%), diabetes mellitus (ESI cohort vs non-ESI cohort, 10.3% vs 9.95%), cancer (ESI cohort vs non-ESI cohort, 2.22% vs 2.18%), systemic lupus erythematosus (ESI cohort vs non-ESI cohort, 0.08% vs 0.10%), and rheumatoid arthritis (ESI cohort vs non-ESI cohort, 0.08% vs 0.14%). The mean follow-up duration for the outcome of osteoporosis occurrence was 7.15 years (standard deviation [SD] = 3.22 years) for the ESI cohort and 7.34 years (SD = 3.36 years) for the non-ESI cohort (Table 1).

Overall, the incidence density rates of osteoporosis were 79.5 and 70.1 per 10,000 PY for the ESI and non-ESI cohorts, respectively (Table 2). Osteoporosis risk was significantly higher in the female population than in the

male population (adjusted hazard ratios [aHR] = 2.93, 95% CI = 2.44-3.53, *P* = 0.0001). Relative to that in the youngest group (20-39 years), osteoporosis risk was significantly higher in the groups aged 40-64 years (aHR = 15.2, 95% CI = 9.77-23.6, *P* = 0.0001) and ≥ 65 years (aHR = 52.2, 95% CI = 33.1-82.4, *P* = 0.0001) (Table 2).

Table 1. *Baseline characteristics of patients.*

	ESIs				*P* value
	Yes (n = 4,957)		No (n = 4,957)		
	N	%	N	%	
Gender					0.87
Men	2,944	59.4	2,905	59.6	
Women	2,013	40.6	2,052	40.4	
Age					0.38
20-39	2,231	45.0	2,214	44.7	
40-64	1,618	32.6	1,677	33.8	
≥ 65	1,108	22.4	1,066	21.5	
mean (SD)					
Urbanization Level					0.30
1 (highest)	1,426	28.8	1,407	28.4	
2	1,432	28.9	1,479	29.8	
3	974	19.7	910	18.4	
4 (lowest)	1,125	22.7	1,161	23.4	
Occupation					0.73
White Collar	2,587	52.2	2,548	51.4	
Blue Collar	1,908	38.5	1,938	39.1	
Others	462	9.32	471	9.50	
Comorbidity					
Liver Cirrhosis	1,209	24.4	1,171	23.6	0.37
Hypertension	1,464	29.5	1,448	29.2	0.72
Diabetes Mellitus	510	10.3	493	9.95	0.57
Chronic Kidney Disease	73	1.47	75	1.51	0.87
Coronary Artery Disease	801	16.2	758	15.3	0.24
COPD	954	19.3	917	18.5	0.34
Anxiety	653	13.2	615	12.4	0.25
Depression	271	5.47	259	5.22	0.59
Epilepsy	41	0.83	39	0.79	0.82
Cerebrovascular Disease	423	8.53	417	8.41	0.83
Cancer	110	2.22	108	2.18	0.89
Systemic Lupus Erythematosus	4	0.08	5	0.10	0.74
Rheumatoid Arthritis	4	0.08	7	0.14	0.37

*P value < 0.05 as statistically significance.
Abbreviation: ESIs: epidural steroid injections.

In the competing risk regression model adjusted for age, gender, and comorbidities, the ESI cohort still exhibited a significantly higher osteoporosis risk relative to the non-ESI cohort (absolute standardized hazard ratio [aSHR] = 1.23, 95% CI = 1.05-1.45, *P* = 0.01; Table 3). A gender-specific comparison of the ESI and non-ESI cohorts revealed that the relative risk of osteoporosis was significant for men (aSHR = 1.35, 95% CI = 1.02-1.80, *P* = 0.04), but nonsignificant for women (aHR = 1.15, 95% CI = 0.94-1.40, *P* = 0.17; Table 3). An age-specific comparison of the ESI and non-ESI cohorts indicated that the relative risk of osteoporosis did not differ significantly among the various age groups. An urbanization-specific comparison of the ESI and non-ESI cohorts revealed that the relative risk of osteoporosis was significantly higher in the group with the lowest urbanization level (fourth level; aSHR = 1.46, 95% CI = 1.10-1.95, *P* = 0.009; Table 3). Among the patients with the lowest socioeconomic status, osteoporosis risk was significantly higher in the ESI cohort than in the non-ESI cohort (aSHR = 1.96, 95% CI = 1.19-3.22, *P* = 0.009; Table 3). A comorbidity-specific analysis indicated that, among the patients without comorbidities, osteoporosis risk was significantly higher in the ESI cohort than in the non-ESI cohort (aSHR = 1.58, 95% CI = 1.08-2.32, *P* = 0.02; Table 3).

Discussion

A review article (12) revealed that use of corticosteroids may provide short-term pain reduction and improvement in the function of the injected joints, but also cause several notable adverse effects. Various types of epidural injections are administered to reduce the symptomatic pain of lumbar disc herniation, and steroid injections have been reported to have more favorable results relative to injections with saline or only local anesthetics in short-term follow-up studies (13,14). However, Shanthanna et al (15) conducted a meta-analysis in 2020, and they discovered that the addition of corticosteroids to a local anesthetic formula for local injections may be potentially harmful while providing only small advantages. Several meta-analyses (16-22) suggested that steroids have adverse effects on symptom relief when it is added to local anesthetics utilized for epidural injections for a cervical or lumbar spine disorder, and they suggested reserving steroids for nonresponsive patients who are under local anesthetics and affected by severe radiculitis. In the present study, the incident rates of osteoporosis were significantly higher in the ESI cohort than in the

Table 2. *Risk of osteoporosis*.

	Event	PY	IR	Crude		Adjusted	
				HR (95% CI)	*P* value	HR (95% CI)	*P* value
ESIs							
No	271	38,678	70.1	1 (reference)		1 (reference)	
Yes	284	35,721	79.5	1.13 (0.96, 1.33)	0.13	1.23 (1.05, 1.45)	0.01*
Gender							
Men	175	29,692	58.9	1 (reference)		1 (reference)	
Women	374	44,669	83.7	1.43 (1.19, 1.71)	< 0.001*	2.93 (2.44, 3.53)	< 0.001*
Age							
20-39	23	36,128	6.37	1 (reference)		1 (reference)	
40-64	188	25,953	72.4	11.3 (7.36, 17.5)	< 0.001*	15.2 (9.77, 23.6)	< 0.001*
≥ 65	338	12,280	275.2	40.8 (26.7, 62.3)	< 0.001*	52.2 (33.1, 82.4)	< 0.001*
Urbanization Level							
1 (highest)	146	21,523	67.8	1 (reference)		1 (reference)	
2	137	22,252	61.6	0.91 (0.72, 1.15)	0.42	0.96 (0.76, 1.22)	0.74
3	96	14,183	67.7	0.99 (0.77, 1.29)	0.97	1.07 (0.83, 1.39)	0.59
4 (lowest)	170	16,402	103.6	1.51 (1.21, 1.88)	< 0.001*	1.24 (0.98, 1.58)	0.08
Occupation							
White Collar	224	39,489	56.7	1 (reference)		1 (reference)	
Blue Collar	265	28,331	93.5	1.64 (1.37, 1.95)	< 0.001*	0.99 (0.81, 1.20)	0.88
Others	60	6,541	91.7	1.59 (1.19, 2.11)	0.002*	1.26 (0.94, 1.69)	0.13

Abbreviations: ESIs: epidural steroid injections; IR: incidence rate, per 10,000-PY; PY: person-years; HR: hazard ratio; CI: confidence interval.
The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.
Other occupations included primarily retired, unemployed, or low-income populations.
Model was adjusted by gender, age, urbanization level, occupation, comorbidities, and medications listed in Table 1.
*P value < 0.05 as statistically significance.

non-ESI cohort. In the competing risk regression model adjusted for age, gender, and comorbidities, the risk of osteoporosis was still significantly higher in the ESI cohort than in the non-ESI cohort (aSHR = 1.23, 95% CI = 1.05-1.45, P = 0.01; Table 3). Although Kang et al (23) reported that ESIs with a maximum cumulative triamcinolone dose of 200 mg per year may be safe, studies (23-27) have increasingly demonstrated that ESIs may adversely affect bone health by interfering with normal bone metabolism, thereby increasing the risk of fractures. Another 2 prospective studies (28,29) revealed that postmenopausal women who had received either a single ESI dose with 80-mg triamcinolone or multiple ESIs with a cumulative triamcinolone dose of > 200 mg experienced a decrease in the BMD of the hip and an increase in the serum markers for bone turnover. In an updated trend review, Bicket et al (30) revealed that the synthetic steroids commonly used in epidural injections typically contain particulate preparations that allow for aggregation into nonsoluble small particles (31,32). Furthermore, in a large retrospective cohort study (33), 3,000 patients with spinal pain who received lumbar ESIs were matched with 3,000 similar patients who did receive such injections, and the results indicate that each ESI increased fracture risk by 21%.

Appropriate preventive management can reduce the risk of osteoporotic fracture in patients undergoing steroid treatments (34). In a study (35), the cessation of oral corticosteroid treatment reduced the risk of fracture to baseline levels regardless of the cumulative dose of steroids. Because bisphosphonates have a greater effect on cancellous bone than on cortical bone, the changes between baseline and follow-up BMD are greater in the spine than in the femur (36). Furthermore, in several studies (37-39), bisphosphonate was reported to be the most effective antiosteoporosis medication for treating glucocorticoid-induced osteoporosis and preventing osteoporotic fracture. That is, ESI recipients who did not take antiosteoporosis medication experienced a considerable reduction in BMD;

Table 3. *Risk of osteoporosis stratified by gender, age, urbanization level, occupation, and comorbidity.*

	ESIs									
	Yes			No			Crude		Adjusted	
	Event	PY	IR	Event	PY	IR	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Overall	284	35,721	79.5	271	38,678	70.1	1.13 (0.96, 1.32)	0.13	1.23 (1.05, 1.45)	0.01*
Gender										
Men	100	14,138	70.7	83	15, 496	53.6	1.28 (0.97, 1.69)	0.09	1.35 (1.02, 1.80)	0.04*
Women	184	21,584	85.3	188	23,183	81.1	1.06 (0.88, 1.29)	0.53	1.15 (0.94, 1.40)	0.17
Age										
20-39	11	17,654	6.23	10	18,606	5.37	1.28 (0.57, 2.87)	0.54	1.35 (0.59, 3.06)	0.48
40-64	96	12,332	77.8	94	13,509	69.6	1.24 (0.94, 1.62)	0.13	1.23 (0.93, 1.62)	0.14
≥ 65	177	5,735	308.7	167	6,562	254.5	1.16 (0.95, 1.42)	0.15	1.22 (0.99, 1.50)	0.06
Urbanization Level										
1 (highest)	70	10,443	67.0	76	11,192	67.9	1.04 (0.77, 1.42)	0.79	0.91 (0.66, 1.25)	0.56
2	68	10,375	65.6	68	11,573	58.8	1.23 (0.89, 1.70)	0.20	1.16 (0.84, 1.61)	0.36
3	53	7,171	73.9	45	7,070	63.7	1.23 (0.84, 1.82)	0.29	1.49 (1.01, 2.22)	0.047*
4 (lowest)	93	7,733	120.3	82	8,843	92.7	1.15 (0.87, 1.51)	0.34	1.46 (1.10, 1.95)	0.009*
Occupation										
White Collar	109	19,178	56.8	113	20,290	55.7	1.06 (0.83, 1.37)	0.63	1.06 (0.82, 1.37)	0.63
Blue Collar	140	13,449	104.1	132	14,868	88.8	1.13 (0.90, 1.42)	0.29	1.23 (0.98, 1.55)	0.23
Others	35	3,094	113.13	26	3,521	73.8	1.54 (0.95, 2.50)	0.08	1.96 (1.19, 3.22)	0.009*
Comorbidity										
No	54	16,376	33.0	45	18,263	24.6	1.15 (0.79, 1.67)	0.47	1.58 (1.08, 2.32)	0.02*
Yes	230	19,346	118.9	226	20,416	110.7	1.07 (0.89, 1.27)	0.48	1.17 (0.98, 1.40)	0.08

Abbreviations: ESIs: epidural steroid injections; IR: incidence rate, per 10,000-person years; PY: person-years; HR: hazard ratio; CI: confidence interval.
The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.
Other occupations included primarily retired, unemployed, or low-income populations.
Comorbidity: Patients with any one of the comorbidities in Table 1 were classified as the comorbidity group.
Model was adjusted by gender, age, urbanization level, occupation, and comorbidities listed in Table 1.
*P value < 0.05 as statistically significance.

whereas, the patients who took antiosteoporosis medication did not experience significant changes in BMD (28); in postmenopausal women, a single ESI reduced BMD by an average of 1.8% and increased their bone turnover rate. Appropriate preventive management can reduce the risk of osteoporotic fracture in patients undergoing steroid treatments (40,42).

In the present study, the major comorbidities affecting the cohort were hypertension, liver cirrhosis, COPD, coronary artery disease, anxiety, and diabetes. Several studies (42-45) have indicated that various comorbidities with high incidence rates are associated with decreased BMD or an increased fracture risk. Park et al (42) reported a high association between osteoporosis and hypertension, and epidemiological and biological studies (43) have supported the theory that osteoporosis and hypertension exhibit the same etiologies and genetic factors. In a meta-analysis, Lupoli et al (44) reported an increased prevalence of osteoporosis in patients with cirrhosis in addition to significantly reduced lumbar spine BMD and Z-scores. In a review, Inoue et al (45) revealed a high prevalence of osteoporosis among patients with COPD. A meta-analysis (46) revealed that the use of inhaled glucocorticoids or inhaled corticosteroids (ICSs) is associated with a modest but significant increase in fracture risk (odds ratios of 1.27 and 1.21 for randomized controlled trials and observational studies, respectively) in patients with COPD. By contrast, Liu et al (11) reported that ICSs had a dose-response protective effect for osteoporosis in women with COPD; they stated that the cumulative probability for osteoporosis was

significantly lower among ICS users than among ICS nonusers. Furthermore, although the mechanism underlying the association between COPD severity and vitamin D deficiency is unclear, the vitamin D deficiency of patients with COPD has been speculated to be related to decreased sunlight exposure, poor diet, and smoking (47). Lee et al (48) investigated the relationship between coronary artery disease and osteoporosis using dual-energy x-ray absorptiometry (DEXA); they reported that high coronary artery calcium scores and obstructive coronary artery disease indicated using multidetector computed tomography were associated with osteoporosis in asymptomatic postmenopausal women and that this association was independent of cardiovascular risk factors and age. In a population-based retrospective cohort study, Hong-Jhe et al (49) reported that osteoporosis risk was significantly higher in patients with an anxiety disorder (AD) than in patients without an AD after adjusting for potential confounding factors. They also discovered that the risk ratio of osteoporosis was the highest during the one year following the diagnosis of anxiety, but remained significant for > one year. This finding may be attributed to several factors. First, the inflammatory process caused by an AD may trigger the production of inflammatory cytokines and chemokines, which are associated with high rates of bone turnover and bone mass loss (50). Second, the high plasma cortisol levels of patients with an AD may cause osteoporosis. The adrenal glands of patients with an AD may produce substantial amounts of cortisol (51), which reduces bone apposition and increases bone resorption (52). Diabetes is often associated with various skeletal disorders and chronic hyperglycemia can cause the accumulation of advanced glycation end products, which further contribute to a reduction in BMD that reduces bone strength (53).

In a population-based study, Høiberg et al (54) reported that a low Charlson comorbidity score was associated with a higher treatment initiation, but lower adherence and persistence with respect to antiosteoporosis treatment; numerous patients (31.7%) who were advised to initiate treatment did not follow this advice; that is, the patients without comorbidities might have lacked the motivation and willingness to adhere to further follow-up and osteoporosis management after their symptoms were relieved through the procedures that they underwent.

After adjustments were made for urbanization level in the present study, the relative risk of osteoporosis was significantly higher in the group with the lowest urbanization level (fourth level; aSHR = 1.46, 95% CI = 1.10-1.95, P = 0.009; Table 3). Several studies (55-59) have attempted to clarify the association between residential area and osteoporosis. A review study (55) conducted in southern Sweden revealed that urban residents had lower bone mineral content relative to rural residents; whereas, another study (56) conducted in eastern Poland did not detect a significant difference in BMD between urban and rural residents. However, a cross-sectional study by Kim et al (57) indicated that individuals in rural single-person households had significantly lower BMD levels and greater odds of developing osteoporosis in the lumbar spine relative to individuals from urban households with 2 or more individuals; this finding may be related to the benefits of osteoporosis screening, which is more accessible for urban residents. Furthermore, Jandoc et al (58) examined a Canadian population from the Ontario Drug Benefit Formulary, and they discovered that a significantly lower proportion of oral bisphosphonate formulations (alendronate + vitamin D3) were dispensed in rural regions than in urban regions. Romero et al (59) compared multiple population centers (rural vs urban), and they reported that relative to postmenopausal women living in urban regions, those living in rural regions were poorer and had lower vitamin D levels, lower BMD in the lumbar spine, and higher prevalence rates of vertebral fractures and osteoporosis. The results of these studies and our findings suggest that compliance with appropriate osteoporosis management following ESIs is a crucial factor that influences the occurrence of osteoporosis and the future risk of fragility fractures, especially for individuals living in low urbanization regions or those with low socioeconomic status.

The aSHR (aSHR = 1.96, 95% CI = 1.19-3.22, P = 0.009) for receiving epidural injections relative to not receiving such injections was revealed to be significantly higher in the other-occupations subgroup, which mostly comprised retired, unemployed, and low-income populations (Table 3). That is, receiving ESIs leads to more associated risk of osteoporosis in this occupation subgroup than in the overall population even after adjustments for gender, age, urbanization level, and other comorbidities. In other words, this occupational subgroup, which represents a low-income population, is vulnerable to the risk of osteoporosis associated with receiving epidural injections. Given that antiosteoporosis medication was reported to be effective for treating glucocorticoid-induced osteopo-

rosis and preventing osteoporotic fracture, appropriate preventive management can reduce the risk of osteoporosis after receiving steroid treatments. These phenomena may be explained by the vulnerability of low-income populations to the osteoporotic risk associated with various factors. First, low socioeconomic status, poor nutritional status, and low educational level are associated with the risk of osteoporosis in postmenopausal women and older men (10,60,61). The literature has concluded that long-term medication adherence influences compliance with the use of antiosteoporotic agents and interferes with protective effects against the associated osteoporotic risk. Second, given the limited budget for providing health care or commercial insurance to unemployed or retired populations, further reimbursement for the antiosteoporotic agents used after epidural procedures may become a financial factor that influences long-term adherence. Third, engagement in part-time jobs or labor work with insufficient employment security may increase the physical burden or osteoporotic injury risk for patients with a low-income level. In conclusion, even after stratification was performed for gender, age, urbanization level, and comorbidities, low-income populations (e.g., primarily retired or unemployed populations) still exhibited a higher osteoporotic injury risk relative to other populations for several reasons. Therefore, this finding highlights the value of clinical decision-making for epidural injections, especially in populations that lack supporting resources for accessing subsequential antiosteoporosis medication.

Limitations

This study has several limitations. First, the NHIRD does not provide detailed information regarding DEXA results for femoral neck or lumbar spine, estimated glomerular filtration rate (i.e., chronic kidney disease), systolic and diastolic blood pressure, smoking habit, pulmonary function, activities of daily living, dietary preference, and exercise habits. Second, the linear association between the dosage of steroids injected and the increasing risk of osteoporosis was not fully clarified in the present study. Further research should focus on the correlation of cumulative doses of steroids with an increased risk of osteoporosis and fragility fractures and the relationship of such doses with various risk factors.

Conclusions

The present study revealed that administering ESIs to patients with lumbar spondylosis is associated with a high risk of osteoporosis. Furthermore, the results of this population-based retrospective cohort study can enhance the clinical awareness of the increasing risk associated with high-satisfaction palliative procedures. This finding is particularly applicable for patients with a low socioeconomic level and those who live in regions with low urbanization. Adequate education that enhances adherence to post-ESI osteoporosis surveys and treatments is crucial for these patients.

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