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Chronic NSAIDs Use Increases the Risk of a Second Hip Fracture in Patients After Hip Fracture Surgery

Evidence From a STROBE-Compliant Population-Based Study

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Abstract: Nonsteroidal anti-inflammatory drugs (NSAIDs) control musculoskeletal pain, but they also cause adverse side effects. The aim of this study is to explore the impact of chronic NSAIDs use on the risk of a second hip fracture (SHFx) after hip fracture surgery.

This population-based case-cohort study used the Taiwan National Health Insurance Research Database (NHIRD), which contains data from >99% of the population. From a random sample of 1 million enrollees, we identified 34,725 patients ≥40 years who sustained a first hip fracture and underwent hip fracture surgery between 1999 and 2009. Chronic NSAIDs use is defined as taking NSAIDs for at least 14 days a month for at least 3 months. The main outcome measure is an SHFx.

Propensity-score matching was used to control for confounding. Our results revealed that chronic NSAIDs use was a significant risk factor for an SHFx in patients after hip fracture surgery and for adverse side effects that might last for 12 months. Compared with the nonchronic-use cohort (n = 29,764), the adjusted hazard ratio of an SHFx was 2.15 (95% CI: 2.07–2.33) for the chronic-use cohort (n = 4961). The 10-year Kaplan–Meier survival analyses showed that chronic NSAIDs use presented a positive year-postsurgery-dependency effect on the risk of an SHFx in all the selected subgroups of patients (all $P \leq 0.011$).

In conclusion, chronic NSAIDs use increases the risk of an SHFx after hip fracture surgery. Avoiding chronic NSAIDs use must be emphasized in clinical practice.

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Abbreviations: CCI = Charlson Comorbidity Index, CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID = Longitudinal Health Insurance Database, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institute, NSAIDs = nonsteroidal anti-inflammatory drugs, OR = odds ratio, PSM = propensity-score matching, SHFx = second hip fracture.

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INTRODUCTION

Elderly patients with fragility hip fractures continued to be at risk for subsequent hip fractures.[1] The 1-year risk of a second hip fracture (SHFx) is substantial and estimated at between 2% and 5%, depending on the age of the patient.[1–3] An SHFx is more deadly than a first hip fracture, but the cumulative mortality rates of a first hip fracture may be higher than that for other well-known life-threatening conditions, such as myocardial infarction and gastric or pancreatic cancer.[4–6] Moreover, this type of fracture is known as the most devastating fracture for elderly patients, is associated with an extremely hard rehabilitation process to go through, and puts a considerable cost burden on the family and society for that condition.[3,7] Therefore, an increasing number of studies have been done to find the best prophylactic strategies for preventing an SHFx in patients after hip fracture surgery.[1–3]

Elderly patients are usually prescribed more drugs than are younger patients because aging is closely associated with a deterioration in health.[8,9] Whether advancing age per se is a cause of increased risk of adverse side effects is still being debated; many studies show a positive correlation between the age and the risk of adverse side effects.[8–10] It has been estimated that 6.5% of hospital admissions are related to adverse side effects of prescription drugs, and that nonsteroidal anti-inflammatory drugs (NSAIDs) are responsible for ~11% of these hospitalizations.[11,12] It is also clear that most adverse side effects that cause hospitalization are type A: dose-related and thus predictable and potentially avoidable.[10] In the previous study,[3] we reported that using NSAIDs was associated with a higher risk of an SHFx, which might be an unrecognized cause of preventable drug-related admissions. Even so, the restriction on NSAIDs use remains to be unclear. Alternative therapies are available for pain management in patients after hip fracture surgery; hence, it is important to determine which are the safest options in terms of subsequent fractures.

The objective of this nationwide population-based observational study was to explore the hypothesis that chronic NSAIDs use contributes to an SHFx in patients after hip fracture surgery. We also determine the effects of gender, age, the Charlson comorbidity index (CCI), and metabolic syndrome (diabetes mellitus, hypertension, and hyperlipidemia) on survival free of an SHFx in patients who do and do not chronically use NSAIDs. The information from this study may be valuable for improving the medical care of elderly patients after hip fracture surgery and for preventing an SHFx and subsequent mortality.

MATERIALS AND METHODS

Data Source

The Taiwan National Health Insurance (NHI) program, a single-payer universal program operated by the Taiwanese

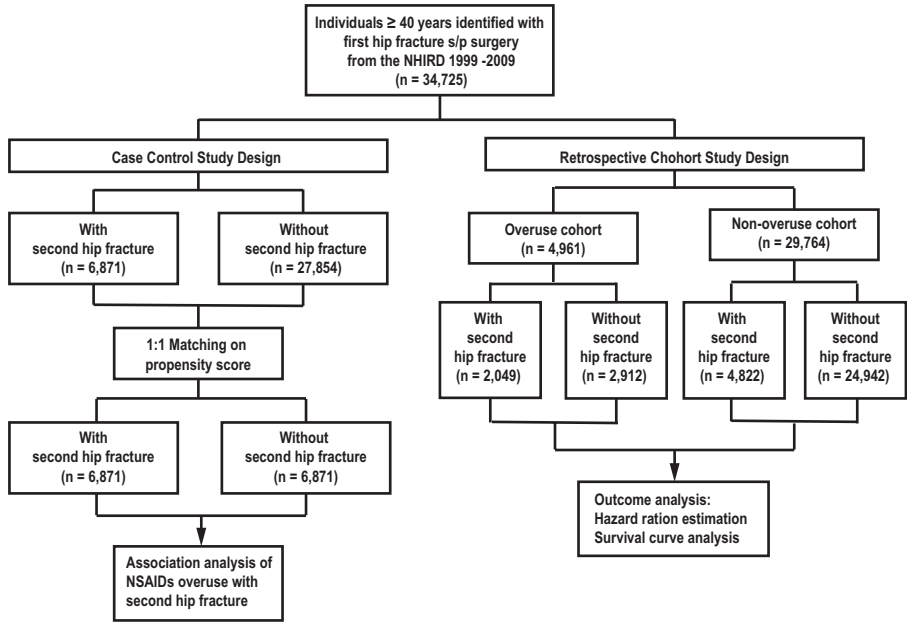

FIGURE 1. A flowchart of the patient selection process and distribution.

government, has enrolled >99% of the population since 2009. After the billing process, the Taiwan National Health Research Institute (NHRI) compiles data from NHI claims and then provides the National Health Insurance Research Database (NHIRD) for research (http://nhird.nhri.org.tw/). The Longitudinal Health Insurance Database (LHID), a representative subset of the NHIRD, contains all the original claim data of 1 million individuals randomly sampled from the Registry for Beneficiaries. Before transferring data to the NHIRD, the government deleted all the identifiers of individual beneficiaries and medical care providers. The accuracy of the NHIRD diagnoses of major disorders has been validated.[13] In the present study, data were obtained from the LHID/NHIRD for analysis.

Study Design and Participants

After being approved by the Institutional Review Board of Chang Gung Memorial Hospital, this nationwide population-based observational study used the LHID/NHIRD registry from January 1999 to December 2009. The inclusion criteria were: (1) a discharge diagnosis code of hip fracture (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnosis codes 820.0–820.9), (2) a procedure code of internal fixation or partial hip replacement (ICD-9-CM procedure codes 79.15, 79.35, and 81.52), and (3) 40 years old or older. The first admission date for a hip fracture was defined as the index date. Nonresidents of Taiwan and those with a diagnosis of hip fracture within 2 years before the index date were excluded to avoid confounding effects. At this stage, 34,725 patients with a hip fracture were included and followed longitudinally until the end of the study. The present study is divided into 2 parts. The first part is a case-control study, intended to identify factors that might contribute to an SHFx in patients after hip fracture surgery. The second part is a retrospective cohort study, intended to obtain additional evidence that supports the hypothesis that chronic NSAIDs use contributes to an SHFx. The flowchart of the patient selection process and distribution is shown in Figure 1.

Primary and Secondary Endpoints

Chronic NSAIDs use is taking NSAIDs for at least 14 days a month for at least 3 months.[14] The primary endpoint of this study was to determine the causal link between chronic NSAIDs use and an SHFx. In the first part of the study, we used the propensity-score matching (PSM)[15,16] to control for potential confounding factors: age, gender, monthly income, urbanization level, the CCI, and other concurrent medication use. In the second part of the study, Cox proportional-hazards regression was used to analyze the effect of chronic NSAIDs use on survival without an SHFx in patients after hip fracture surgery. For our secondary endpoint, the effect of other risk factors on survival without an SHFx was analyzed.

Statistical Analysis

Student *t* tests and χ^2 tests were used to analyze numerical and categorical variables, respectively. After using PSM to control for confounding, between-group comparisons were done by estimating the odds ratio (OR) and the 95% confidence interval (CI) in a logistic regression model. To examine the effect of chronic NSAIDs use on the risk of an SHFx, a Cox proportional-hazards regression model was used. Ten-year survival rates without an SHFx after hip fracture surgery were estimated using the Kaplan–Meier method and the log-rank test. Significance was set at $P < 0.05$ (2-sided). SAS 9.2 (SAS, Inc., Cary, NC) was used for all analyses.

RESULTS

We enrolled 34,725 patients ≥ 40 years old who sustained a first hip fracture and underwent hip fracture surgery between 1999 and 2009 (Figure 1); most of them were women (64.9% vs

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TABLE 1. Characteristics of Patients With or Without a Second Hip Fracture After Their First Hip Fracture Surgery

	Unmatched			Matched		
Variables	**SHFx (n = 6871)**	**Non-SHFx (n = 27,854)**	***P***	**SHFx (n = 6871)**	**Non-SHFx (n = 6,871)**	***P***
Gender, n (%)			0.0043∗			1.0000
Male	2412 (35.10)	12757 (45.80)		2412 (35.10)	2412 (35.10)	
Female	4459 (64.90)	15097 (54.20)		4459 (64.90)	4459 (64.90)	
Age (years), mean ± SD	71.34 ± 6.59	75.91 ± 8.11	0.5071	71.34 ± 6.59	72.80 ± 7.12	0.9486
Age (years), n (%)			0.4595			1.0000
40–49	598 (8.70)	1365 (4.90)		598 (8.70)	598 (8.70)	
50–59	921 (13.40)	2423 (8.70)		921 (13.40)	921 (13.40)	
60–69	1553 (22.60)	6657 (23.90)		1553 (22.60)	1553 (22.60)	
70–79	1738 (25.29)	8022 (28.80)		1738 (25.29)	1738 (25.29)	
≥80	2061 (30.00)	9387 (33.70)		2061 (30.00)	2061 (30.00)	
Monthly income, n (%)			0.8837			0.8865
NTD ≤ 17,280	1477 (21.50)	5404 (19.40)		1477 (21.50)	1475 (21.47)	
NTD 17,281–28,800	1532 (22.30)	8384 (30.10)		1532 (22.30)	1530 (22.27)	
NTD 28,801–45,800	2192 (31.90)	7186 (25.80)		2192 (31.90)	2199 (32.00)	
NTD 45,801–72,800	1402 (20.40)	6128 (22.00)		1402 (20.40)	1411 (20.54)	
NTD ≥ 72,801	268 (3.90)	752 (2.70)		268 (3.90)	256 (3.72)	
Urbanization level, n (%)			0.6245			0.9114
Level 1	1676 (24.30)	5999 (21.51)		1676 (24.30)	1668 (24.28)	
Level 2	2313 (33.67)	9986 (35.85)		2313 (33.67)	2325 (33.83)	
Level 3	1040 (15.14)	5961 (21.40)		1040 (15.14)	1051 (15.30)	
Level 4	1208 (17.58)	3095 (11.11)		1208 (17.58)	1201 (17.48)	
Level 5	260 (3.79)	1287 (4.62)		260 (3.79)	245 (3.57)	
Level 6	293 (4.26)	986 (3.54)		293 (4.26)	299 (4.35)	
Level 7	81 (1.17)	540(1.97)		81 (1.17)	82 (1.19)	
Charlson Comorbidity index, mean ± SD	5.07 ± 1.53	4.78 ± 1.22	0.0100*	5.07 ± 1.53	5.10 ± 1.49	0.8867
Medications, n (%)						
Steroids	1767 (25.72)	3432 (12.32)	<0.0001*	1767 (25.72)	1704 (24.80)	0.6045
Muscle relaxants	364 (5.30)	1050 (3.77)	0.4487	364 (5.30)	359 (5.22)	0.8826
Benzodiazepines	1091 (15.88)	3459 (12.42)	0.4980	1091 (15.88)	1215 (17.68)	0.4531
Antiosteoporotic agents	1931 (28.10)	2727 (9.79)	<0.0001*	1931 (28.10)	1743 (25.37)	0.6680
Propensity score, mean ± SD	0.253 ± 0.012	0.216 ± 0.105	0.0010*	0.253 ± 0.012	0.250 ± 0.019	0.9660

NTD = New Taiwan dollars; SD = standard deviation; SHFx = second hip fracture.
* $P < 0.05$ is significant. All analyses were done using SAS 9.2.

54.2%, $P = 0.0043$) (Table 1). In patients with an SHFx the CCI was significantly >5 (5.07 vs 4.78, $P = 0.010$), more than twice as many were taking steroids (25.7% vs 12.3%, $P < 0.0001$), and almost 3 times as many were taking antiosteoporotic agents (28.1% vs 9.8%, $P < 0.0001$). Age, monthly income, urbanization level, and concurrent use of muscle relaxants and benzodiazepines were not significantly different in patients with and without an SHFx. To clarify the risk association between chronic NSAIDs use and an SHFx, the confounding variables were controlled using PSM. After 1:1 matching, the propensity-score was almost identical in both groups (0.253 vs 0.250, $P = 0.9660$), which confirmed that chronic NSAIDs use, whether Cox-2 inhibitors or nonselective NSAIDs, is a significant time-dependent predictor of an SHFx in patients after hip fracture surgery (Table 2).

The chronic-use cohort contained 4961 patients who chronically used NSAIDs and the nonchronic-use cohort contained 29,764 patients (Figure 1). The follow-up results revealed that the chronic-use cohort was 1.87 times more likely to develop an SHFx than was the nonchronic-use cohort (479.4 vs 191.5 per 10,000 person-years, HR: 1.87, 95% CI: 1.64–2.10) (Table 3). The incidence of an SHFx was greater in women than in men in both cohorts. The gender-specific hazard of an SHFx in the chronic-use cohort relative to that in the nonchronic-use cohort was significant both for women (HR: 2.33, 95% CI: 2.10–2.55) and for men (HR: 1.79, 95% CI: 1.50–1.92). The incidence of an SHFx increased with age in both cohorts. The age-specific hazard of an SHFx in the chronic-use cohort relative to that in the nonchronic-use cohort was significant for patients ≥60 (60–79, HR: 2.24, 95% CI: 1.81–2.65; ≥80, HR: 3.28, 95% CI: 2.93–3.64), but not for patients < 60 (40–59, HR: 0.85, 95% CI: 0.74–1.11). Additionally, the HRs increased with the number of years post hip fracture surgery (Table 3).

Overall, the adjusted HR was 115% higher for patients who chronically used NSAIDs than for those who did not ($P < 0.001$) (Table 4). Compared with patients 40–59 years old, the adjusted HRs of an SHFx were 2.41 (95% CI: 2.16–2.65) in those 60–79 and 3.11 (95% CI: 2.90–3.45) in those ≥80. Compared with male patients, the adjusted HR of an SHFx

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TABLE 2. NSAIDs-Overuse in Matched Patients With or Without a Second Hip Fracture After Their First Hip Fracture Surgery

Variables	SHFx (n = 6871)	Non-SHFx (n = 6871)	Crude OR	95% CI	Adjusted* OR	95% CI
No overuse, n (%)	5162 (75.13)	6006 (87.41)	1.00	Reference	1.00	Reference
Any use, n (%)						
Overuse within 3 months	1394 (20.29)	632 (9.20)	2.38	2.30–2.99	2.25	2.16–2.28
Overuse within 6 months	1532 (22.30)	710 (10.33)	1.99	1.64–2.50	1.62	1.43–1.72
Overuse within 12 months	1709 (24.87)	865 (12.59)	1.76	1.32–1.84	1.59	1.41–1.62
Cox-2 inhibitor use, n (%)						
Overuse within 3 months	986 (14.35)	344 (5.01)	2.71	2.12–3.20	2.44	2.30–2.58
Overuse within 6 months	1082 (15.75)	387 (5.63)	2.59	2.24–2.85	2.25	2.13–2.30
Overuse within 12 months	1156 (16.82)	449 (6.51)	2.28	2.13–2.59	2.07	1.95–2.15
Nonselective NSAIDs use, n (%)						
Overuse within 3 months	408 (5.94)	288 (4.19)	1.23	1.16–1.39	1.12	1.08–1.23
Overuse within 6 months	450 (6.55)	323 (4.70)	1.20	1.14–1.28	1.09	1.03–1.14
Overuse within 12 months	553 (8.05)	416 (6.05)	1.06	1.01–1.13	1.04	1.01–1.07

CI = confidence interval; Cox-2 = cyclooxygenase-2; NSAIDs = nonsteroidal anti-inflammatory drugs; OR = odds ratio; Overuse = drug prescription at least 14 days a month on a regular basis for at least 3 months; SHFx = second hip fracture. $P < 0.05$ is significant. All analyses were done using SAS 9.2.

* Adjusted for the propensity score.

was 1.54 (95% CI: 1.20–1.68) in female patients. Relative to patients with a CCI <5 and those without metabolic syndrome, the adjusted HRs of an SHFx were 3.20 (95% CI: 3.08–3.43) in those with a CCI ≥5, 4.19 (95% CI: 4.03–4.26) in those with diabetes mellitus, 3.28 (95% CI: 3.07–3.43) in those with hypertension, and 1.53 (95% CI: 1.11–1.72) in those with hyperlipidemia, respectively. Finally, the 10-year Kaplan–Meier survival analyses showed that chronic NSAIDs use presented a positive year-postsurgery-dependency effect on the risk of an SHFx in all the selected subgroups of patients (all $P \leq 0.011$) (Figure 2).

DISCUSSION

This population-based case-cohort study showed that chronic NSAIDs use increased the risk of an SHFx in patients after hip fracture surgery. After multiple confounding factors had been adjusted for, we found that chronic NSAIDs use was

TABLE 3. Incidence Density of Second Hip Fracture Estimated by Age, Sex, and Follow-Up Year Between the NSAIDs-Overuse Cohort and the Nonoveruse Cohort

	Overuse				Nonoveruse					
Variables	n	Case	Person-Years	Incidence Rate*	n	Case	Person-Years	Incidence Rate*	Crude HR	95% CI
All	4961	2049	42739	479.4	29764	4822	251803	191.5	1.87	1.64–2.10
Gender										
Female	3082	1402	25780	543.8	17790	2541	132106	207.5	2.33	2.10–2.55
Male	1879	647	16959	381.5	11974	2281	119697	190.6	1.79	1.50–1.92
Age (years)										
40–59	704	187	6986	267.7	4603	1332	44462	299.6	0.85	0.74–1.11
60–79	1942	889	19264	461.5	16028	2402	137542	174.6	2.24	1.81–2.65
≥ 80	2315	973	16489	568.3	9097	1088	69799	155.9	3.28	2.93–3.64
Follow-up years										
<1	5	3	4	7500.0	7	3	6	5000.0	1.13	1.02–1.36
1–2	22	16	43	3721.0	16	7	28	2500.0	1.21	1.05–1.34
2–3	150	44	409	1075.8	88	25	316	791.1	1.30	1.21–1.45
3–4	112	69	657	1050.2	145	52	706	736.5	1.39	1.24–1.42
4–5	4033	1687	35249	478.6	11027	2871	86572	331.6	1.41	1.33–1.51
≥5	639	230	6377	360.7	18481	1864	164175	113.5	2.89	2.76–3.25

CI = confidence interval; HR = hazard ratio; Overuse = drug prescription at least 14 days a month on a regular basis for at least 3 months.

* Incidence Rate, per 10,000 person-years.

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TABLE 4. Adjusted Hazard Ratio and 95% Confidence Intervals of Second Hip Fracture Associated With NSAIDs-Overuse and Covariates

Variables	Crude HR (95% CI)	Adjusted* HR (95% CI)
NSAIDs overuse		
No	1.00 (reference)	1.00 (reference)
Yes	2.49 (2.17–2.63)	2.15 (2.07–2.33)
Age (years)		
40–59	1.00 (reference)	1.00 (reference)
60–79	2.88 (2.43–3.10)	2.41 (2.16–2.65)
≥80	3.27 (2.90–3.45)	3.11 (2.90–3.45)
Gender		
Male	1.00 (reference)	1.00 (reference)
Female	1.73 (1.55–1.86)	1.54 (1.20–1.68)
Charlson comorbidity index		
<5	1.00 (reference)	1.00 (reference)
≥5	3.56 (3.17–3.80)	3.20 (3.08–3.43)
Metabolic syndrome		
Diabetes mellitus (yes vs no)	4.36 (4.01–4.59)	4.19 (4.03–4.26)
Hypertension (yes vs no)	3.35 (3.14–3.60)	3.28 (3.07–3.43)
Hyperlipidemia (yes vs no)	1.72 (1.46–2.05)	1.53 (1.11–1.72)

CI = confidence interval; HR = hazard ratio; NSAIDs = nonsteroidal anti-inflammatory drugs.
* Adjusted for gender, age, Charlson comorbidity index, diabetes mellitus, hypertension, and hyperlipidemia.

associated with an adjusted HR of 2.15 for an SHFx. The association between chronic NSAIDs use and the increased risk of an SHFx was found in all subgroups of patients after hip fracture surgery, especially in female patients, elderly patients, patients with a CCI ≥ 5, and patients with diabetes mellitus, hypertension, or hyperlipidemia. Moreover, the association between chronic NSAIDs use and the risk of an SHFx increased with the number of years after the first hip fracture surgery. To help prevent subsequent hip fractures and associated mortality, NSAIDs after hip fracture surgery should be restricted to situations in which their benefits clearly overweigh their risks and should be prescribed only after potentially safer alternatives have been tried.

To the best of our knowledge, this is the first report to establish a causal relationship between chronic NSAIDs use and an SHFx, and the first to highlight that chronic NSAIDs use might be a neglected cause of preventable hospital admissions because of the adverse side effects of NSAIDs. NSAIDs are widely used because they perform double duty: they are analgesics and, at higher doses, anti-inflammatory drugs.[17,18] Like all medications, they have side effects and might not be right for everyone, particularly for elderly patients.[9,10] In addition to the notoriously increased risks of gastrointestinal bleeding and renal dysfunction they cause,[12,19,20] our results suggested that an SHFx should be added to the list of complications caused by chronic NSAIDs use.

One explanation for the increased risk of an SHFx in patients chronically using NSAIDs is that NSAIDs may directly and adversely affect bone remodeling. NSAIDs, and especially Cox-2 inhibitors, prohibit Cox-2 synthesis, which is necessary to produce inflammatory prostaglandins,[21] and which suppresses cortical bone remodeling without impairing the coupling between bone formation and bone resorption.[21–23] A growing number of studies have suggested that taking NSAIDs may be harmful for bone health. One retrospective study[14] of a cohort of 716,004 cases found that regular use of NSAIDs was associated with a 1.47 relative risk of a nonvertebral fracture and a 2.90 relative risk of a vertebral fracture compared with control patients who did not take NSAIDs. Our data revealed that chronic NSAIDs use increases the risk of an SHFx 2.15 times after hip fracture surgery. Moreover, the adverse side effects of chronic NSAIDs use may last for 12 months.

Another explanation is that patients who overuse NSAIDs might have a higher risk of falls, which subsequently increases the risk of an SHFx. A number of factors that have been identified as risk factors for falls are also associated with hip fractures.[24] Falls are ascribable to a combination of intrinsic and extrinsic factors.[25] The intrinsic factors are an age-related physical decline of, or pathologies affecting, the balance system. The extrinsic factors are environmental circumstances that contribute to falls, or activities with a high risk associated with falls. Although we used PSM to control for most of the intrinsic factors (age, gender, socioeconomic status, comorbidities, and medication use), we did not specifically look at the surgical quality and the extrinsic factors in the present study. Therefore, additional studies are necessary to clarify the effects of these variables on the risk of falls and an SHFx in patients after hip fracture surgery.

The association between metabolic syndrome and osteoporosis has been extensively studied, but results are inconsistent and sometimes contradictory.[26–28] Our results suggested that the main components of metabolic syndrome, all lifestyle diseases themselves, might be another set of risk factors for an SHFx in patients after hip fracture surgery. Diabetes mellitus is the most significant of these factors: its adjusted HR is 4.19, higher than that of hypertension or hyperlipidemia. Because the prevalence of diabetes mellitus has increased dramatically over the past 30 years,[29,30] a clearer understanding of the mechanisms of diabetes mellitus and hip fractures is necessary.

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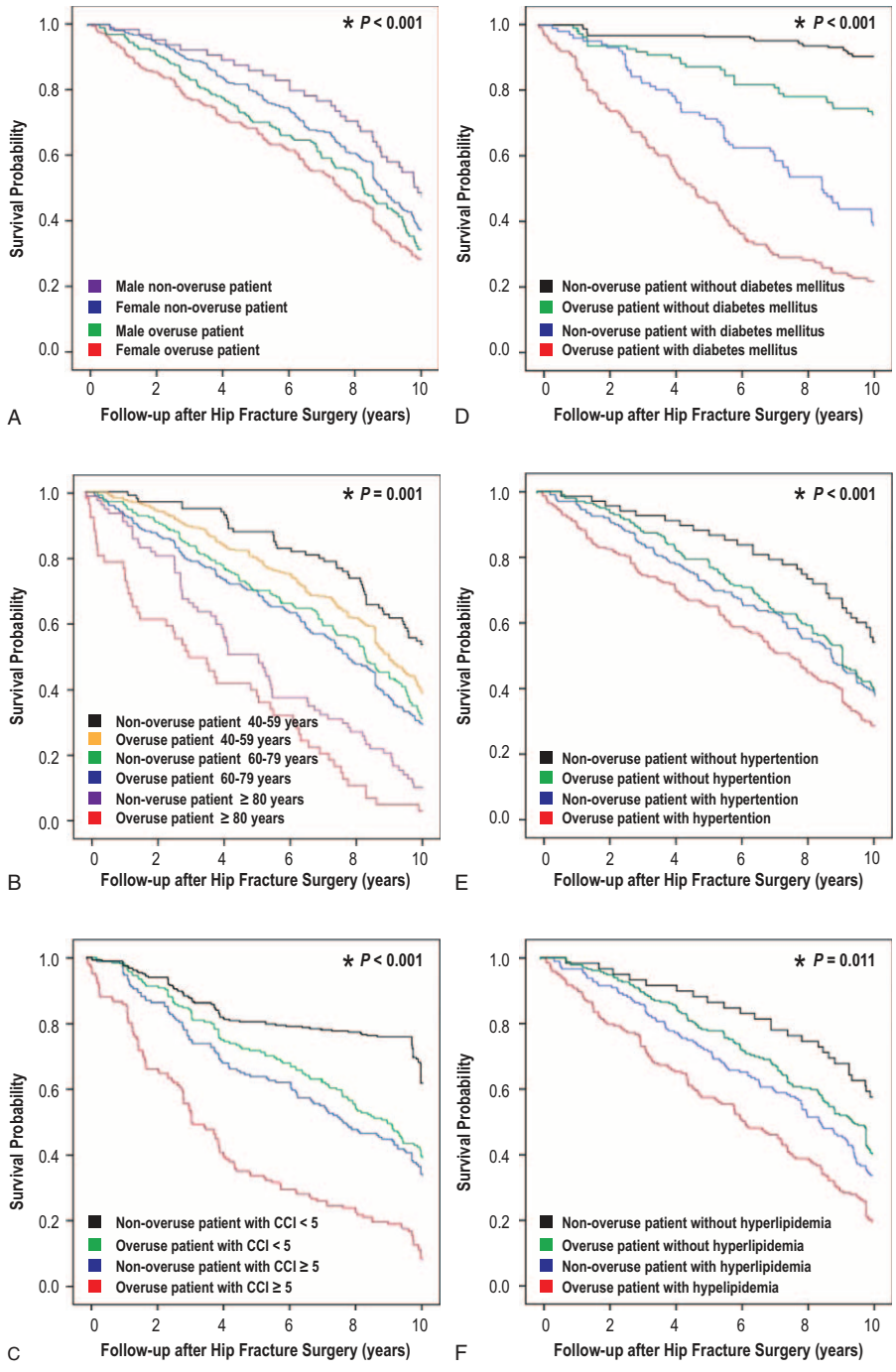

FIGURE 2. Kaplan–Meier survival estimates with a second hip fracture (SHFx) as an endpoint. Survival free of an SHFx for (A) male and female patients who did and did not chronically use NSAIDs, (B) patients of different age groups who did and did not chronically use NSAIDs, (C) patients with and without many comorbidities who did and did not chronically use NSAIDs, (D) patients with and without diabetes mellitus who did and did not chronically use NSAIDs, (E) patients with and without hypertension who did and did not chronically use NSAIDs, and (F) patients with and without hyperlipidemia who did and did not chronically use NSAIDs. $^{*}P < 0.05$. SHFx = second hip fracture, NSAIDs = nonsteroidal anti-inflammatory drugs.

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Our study has some strength. The study participants were collected from the NHIRD, which is population-based, highly representative, and with little room for recall and selection biases. The NHIRD allowed us to identify a large cohort of hip fracture patients with good generalizability. In addition, with the inclusion of 34,725 patients after hip fracture surgery with a follow-up of up to 11 years in the analysis, we were able to demonstrate the greater risk of an SHFx in patients chronically using NSAIDs, a risk that might be overestimated or underestimated in a smaller study.

The study also has some limitations. First, it is retrospective. Second, we could not determine the body mass index, bone mineral density, lifestyle, joint functionality or condition, level of physical activity, or quality of life, which might also have confounded the study results. Lastly, we had no information on study participants' histories of hip fracture 2 years before the index date, which could spuriously underestimate the incidence rate of an SHFx of the study population, but it would have had little influence on the risk estimates of an SHFx associated with chronic NSAIDs use.

In conclusion, this retrospective case-cohort study provides nationwide population-based evidence that chronic NSAIDs use caused an increased risk of an SHFx in patients after hip fracture surgery. Our results suggest that using NSAIDs in patients after hip fracture surgery should be restricted to situations in which the benefits clearly overweigh the risks and should be prescribed only after potentially safer alternatives have been tried. It is necessary to emphasize the avoidance of chronic NSAIDs use in clinical practice in order to prevent adverse side effects, such as a subsequent hip fracture and its associated mortality.

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