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Use of corticosteroids is not associated with repeated vertebroplasty or kyphoplasty within one year after the surgery in patient older than 50 years

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ABSTRACT

Objective: The aim of this study was to investigate whether corticosteroid use increases the incidence of repeated PVP or kyphoplasty patients older than 50 years.
Methods: This study enrolled the data of 2,753 eligible patients from the Taiwan National Health Insurance Research Database who were exposed to systemic corticosteroids for at least 3 months during the first year preceding the first PVP or kyphoplasty. These steroid users were matched 1:1 in age, sex, and the index date of surgery with non-user controls during the enrollment period.
All patients were followed for 1 year after the first PVP or kyphoplasty. The incidence of repeated PVP or kyphoplasty was compared between the steroid users and controls. A Cox proportional hazards model was developed to account for multiple confounding factors.
Results: The number of patients receiving repeated PVP or kyphoplasty was 233 (8.46%) and 205 (7.45%) in the corticosteroid and control groups, respectively. The Cox proportional hazards model revealed no association between corticosteroid use and repeated PVP or kyphoplasty.
Conclusions: Systemic corticosteroid use for longer than 3 months is not associated with repeated PVP or kyphoplasty within one year of surgery in patient older than 50 years old.
Level of evidence: Level III, Therapeutic study.

Introduction

Vertebral compression fractures (VCFs) significantly deteriorate quality of life and increase mortality in elderly people.[1,2] VCFs are estimated to affect 44 million Americans with an annual healthcare cost of 440 million dollars.[3,4] The morbidities of VCFs include back pain, decreased ambulation, prolonged bed rest, decreased pulmonary function, and decreased ability to live independently.[4,5] Percutaneous vertebroplasty (PVP) or kyphoplasty is effective and safe for patients with painful osteoporotic VCFs and persistent pain. Pain relief after PVP or kyphoplasty is immediate, sustained for at least 1 year, and is significantly greater than that achieved using conservative treatment.[6] However, previous studies have reported that patients receiving PVP or kyphoplasty have a greater risk of new-onset VCFs than that of patients with prior VCFs who did not undergo either procedure.[7,8] Most new adjacent VCFs occur within 3 months following PVPs or kyphoplasties[9,10] and new VCFs could occur repeatedly within a few years after PVP or kyphoplasties, if the steps for prevention of VCFs are not immediate and effective.[8–11] The rate of new VCF occurrence was reported to reach 50% in patients with VCFs.[12,13]

Patients with symptomatic new VCFs can benefit from PVP or kyphoplasty[14,15] with respect to pain relief and functional improvement. PVP cannot prevent further fracture. Prevention of

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further fracture while treating severe osteoporotic VCFs is crucial. Therefore, recognizing and managing the risk factors for VCFs or new VCFs is critical. Risk factors for VCFs include steroid use, prior VCFs, smoking, the female sex, and local kyphosis.[16–18] Possible risk factors for new VCFs after PVP or kyphoplasty include chronic oral steroid use, osteoporosis,[19] and the treatment level being the thoracolumbar junction.[20]

To clarify how corticosteroid use might increase the rate of new VCFs after PVP or kyphoplasty and cause the need for repeating these procedures, we determined the incidence of and calculated the multivariate-adjusted hazard ratio for repeated PVPs or kyphoplasties in a 1-year study period after the first PVP or kyphoplasty for patients with and without exposure to corticosteroids in this population-based cohort study.

Materials and methods

Study design and data source

This was a retrospective cohort study based on an analysis of the National Health Insurance Research Database (NHIRD). The Ministry of Health and Welfare has conducted the National Health Insurance (NHI) program since 1995 to cover the healthcare of 22.9 million residents in Taiwan. More than 99% of the national population is covered by this program. In the NHIRD, diseases are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Data acquisition for this study was approved by the Taiwan NHRI and the study protocol was approved by the institutional review board of E-Da Hospital.

Definition of the study cohorts and outcomes

In this study, we analyzed the NHIRD to identify study cohorts. Patients with osteoporosis receiving antiresorptive agents, such as bisphosphonate, hormone therapy, and teriparatide, who had received PVP or kyphoplasty for the first time were enrolled in this study (Fig. 1). PVP or kyphoplasty surgeries were done by either unilateral or bilateral approach. Patients exposed to systemic corticosteroid therapy for at least 3 months during the previous year before receiving PVP or kyphoplasty for the first time were enrolled in the corticosteroid group. Patients who did not receive any steroid treatment in the previous year before receiving PVP or kyphoplasty for the first time were enrolled in the control group. The index date for baseline matching and outcome observation was assigned as the date when PVP or kyphoplasty was performed for the first time. The steroid users were then matched 1:1 according to age, sex, and the index date with controls who were not exposed to any dosage of a corticosteroid during the study period. Patients aged <50 years and those who used steroids for less than 3 months were excluded from the study. All patients were followed for 1 year after the first PVP or kyphoplasty was performed. Comorbidities were classified as those existing prior to the first PVP or kyphoplasty, according to Charlson's score.[21] Repeated PVP or kyphoplasty was recorded in both groups and used for calculation.

Statistical analysis

Continuous variables were summarized as the mean and standard deviation, and categorical variables as the number and proportion. To determine whether corticosteroids were an independent factor predicting repeated PVP or kyphoplasty, multivariate-adjusted hazard ratios (HRs) were calculated using a Cox proportional hazards model. All data management and HR calculations were performed using the SAS system (version 9.4; SAS Institute, Cary, NC). The calculated results were expressed as a ratio along with 95% confidence intervals (CIs). P values lower than 0.05 were defined as significant in all statistical tests.

Results

Baseline characteristics of the study population

In total, we screened 28,448 patients received PVP or kyphoplasty. Among those patients, 494 cases with age younger than 50 year old and 14,757 cases with systemic corticosteroid therapy for less than 3 months were excluded. There were 4668 patients with systemic corticosteroid therapy for more than 3 months and 8529 patients without steroid therapy. After 1:1 matching in this study, 5506 patients who were eligible for the study (Fig. 1). The corticosteroid and control groups contained 2753 patients each. The study included 1714 male and 3792 female patients. The baseline characteristics and comorbidities of the 5506 patients are listed in Table 1.

Repeated PVP or kyphoplasty between the study cohorts

The number of patients receiving repeated PVP or kyphoplasty was 233 (8.46%) and 205 (7.45%) in the corticosteroid group and control group, respectively (Table 1). A Cox proportional hazards model revealed no association between corticosteroid use and repeated PVP or kyphoplasty.

The multivariate-adjusted model demonstrated that diabetes and malignant tumors were associated with an increased rate of repeated PVP or kyphoplasty (adjusted HR, 0.77; 95% CI, 0.61–0.960 and 0.39; 95% CI, 0.19–0.82, respectively; $P < 0.05$) (Table 2). In the unadjusted analysis, dementia, connective tissue disease, and diabetes with end organ damage were associated with repeated PVP or kyphoplasty (HR, 0.64; 95% CI, 0.43–0.95, 1.34; 95% CI, 1.03–1.75, and 0.61; 95% CI, 0.40–0.91, respectively); however, this association was nonsignificant in the multivariate-adjusted Cox proportional hazard model (Table 2). The relationships between comorbidities and repeated PVP or kyphoplasty are shown in a forest plot (Fig. 2).

Discussion

Corticosteroids can cause adverse effects after long-term use. One possible adverse effect of the usage of corticosteroids is bone mass loss, especially of the trabecular bone (the predominant bone type in the vertebrae).[22] Bone mass loss is more pronounced in the first month after therapy and 10%–20% trabecular bone loss occurs in the first 6 months after therapy. Annual bone mass loss of 2% occurs in the subsequent years. In addition, the loss of cortical bone (at a greater proportion in long bones) occurs at a rate of 2%–3% in the first year. Subsequently, slow and continuous loss of cortical bone persists.[23] The bone mineral density (BMD) decreases significantly after the receipt of a dose of prednisone $\geq$7.5 mg for 3 months.[23] Therefore, the fracture risk is expected to increase after glucocorticoid administration for 3–6 months.[24] In addition, a clinical study reported that the incidence of vertebral and nonvertebral fractures increases by approximately 30%–50% in patients using corticosteroids for >3 months.[23] Furthermore, the risk of fracture for the same BMD is higher in glucocorticoid-induced osteoporosis than in postmenopausal or senile osteoporosis.[25]

Approximately 33% of patients on glucocorticoids have fractures, mainly in the vertebrae, and only 30% of such fractures are symptomatic.[26] A previous population database study in the United Kingdom showed that the risk of fractures, mainly vertebral fractures,[27] significantly increased in patients using glucocorticoids. Some studies have reported that risk factors for VCFs include

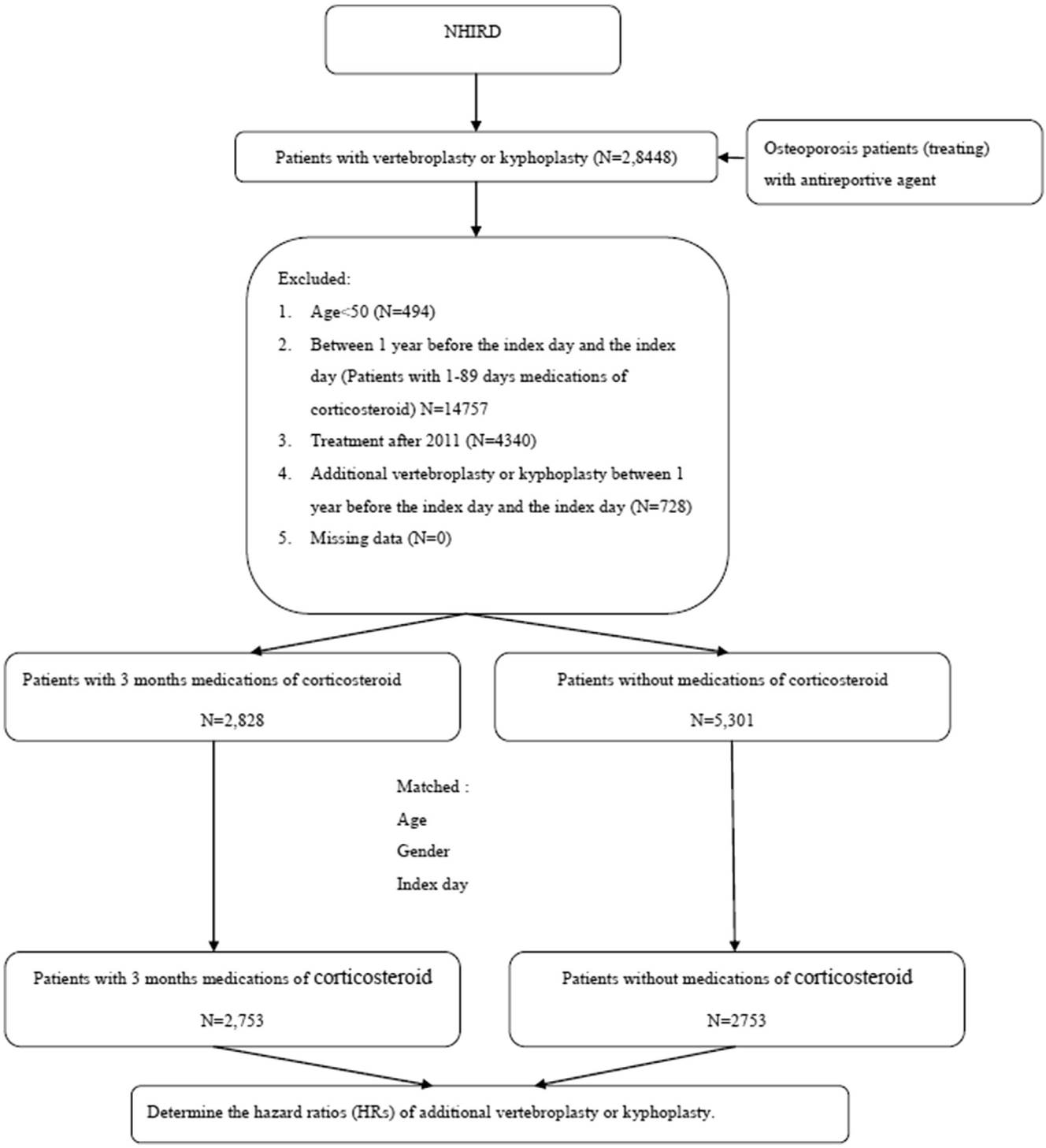

Fig. 1. Flowchart of this study.

steroid use, smoking, the female sex, and older age.[28–31] The effect of glucocorticoids might persist for a long time and cause further harm to the patients. In recent years, the long time usage of steroid with systemic or local epidural forms were documented to lead to increase bone fragility, rapid bone loss and fracture risk (mainly vertebral fractures).[32–34] Therefore, the incidence of refracture in patients with steroids might be higher than that in patients with primary osteoporosis[35,36] and could be a predictor of additional symptomatic VCFs.[19] However, other studies have revealed the opposite outcome and found no association between subsequent fractures and steroid use.[37] In our study, the repeated PVP or kyphoplasty rates were 8.46% and 7.45% in the corticosteroid and control groups, respectively. We found that glucocorticoid use did not affect the number of repeated PVPs or kyphoplasties required. This result may be attributable to patients older than 50 years old with osteoporosis being equally prone to vertebral refracturing. Thus, patients using steroids do not require particular attention, and focus must be placed on treating osteoporosis.

Table 1
Characteristics of the study subjects.

	Non- corticosteroid N = 2753	corticosteroid N = 2753	p-value
Age	74.8 ± 8.29	74.8 ± 8.21	0.9999
Age group			
50-59	163 (5.92)	155 (5.63)	0.8274
60-79	1816 (65.96)	1835 (66.65)	
>=80	774 (28.11)	763 (27.72)	
Gender			
Female	1896 (68.87)	1896 (68.87)	1.0000
Male	857 (31.13)	857 (31.13)	
CCI			
0	313 (11.37)	74 (2.69)	<0.0001
1	535 (19.43)	243 (8.83)	
2	561 (20.38)	487 (17.69)	
2+	1344 (48.82)	1949 (70.8)	
Comorbidities			
Myocardial infarct	109 (3.96)	138 (5.01)	0.0590
Congestive heart failure	428 (15.55)	833 (30.26)	<0.0001
Peripheral vascular disease	132 (4.79)	219 (7.95)	<0.0001
Cerebrovascular disease	952 (34.58)	980 (35.60)	0.4291
Dementia	280 (10.17)	234 (8.50)	0.0331
Chronic lung disease	1248 (45.33)	1907 (69.27)	<0.0001
Connective tissue disease	124 (4.50)	519 (18.85)	<0.0001
Ulcer	1536 (55.79)	2059 (74.79)	<0.0001
Chronic liver disease	626 (22.74)	840 (30.51)	<0.0001
Diabetes	948 (34.44)	1073 (38.98)	0.0005
Diabetes with end organ damage	230 (8.35)	250 (9.08)	0.3393
Hemiplegia	112 (4.07)	87 (3.16)	0.0711
Moderate or severe kidney disease	323 (11.73)	510 (18.53)	<0.0001
Tumor, leukemia, lymphoma	381 (13.84)	602 (21.87)	<0.0001
Moderate or severe liver disease	36 (1.31)	37 (1.34)	0.9062
Malignant tumor, metastasis	50 (1.82)	173 (6.28)	<0.0001
AIDS			
EVENT	205 (7.45)	233 (8.46)	0.1632

Table 2
Prediction for REFRACTURE.

	Crude		Adjusted	
	HR (95% C.I.)	p-value	HR (95% C.I.)	p-value
Corticosteroid vs. Non-corticosteroid	1.14 (0.95–1.38)	0.1628	1.11 (0.91–1.37)	0.3109
Comorbidities				
Myocardial infarct	0.80 (0.48–1.31)	0.3716	0.85 (0.51–1.41)	0.5352
Congestive heart failure	0.90 (0.72–1.13)	0.3792	0.92 (0.72–1.17)	0.4987
Peripheral vascular disease	0.81 (0.53–1.24)	0.3368	0.90 (0.59–1.38)	0.6243
Cerebrovascular disease	0.84 (0.69–1.03)	0.0999	0.93 (0.75–1.15)	0.5175
Dementia	0.64 (0.43–0.95)	0.0260	0.67 (0.45–1.01)	0.0535
Chronic lung disease	1.10 (0.91–1.33)	0.3377	1.11 (0.91–1.37)	0.3053
Connective tissue disease	1.34 (1.03–1.75)	0.0296	1.26 (0.96–1.66)	0.0980
Ulcer	1.11 (0.91–1.35)	0.3053	1.08 (0.88–1.34)	0.4573
Chronic liver disease	1.11 (0.90–1.36)	0.3457	1.15 (0.92–1.42)	0.2193
Diabetes	0.72 (0.58–0.88)	0.0015	0.77 (0.61–0.96)	0.0206
Diabetes with end organ damage	0.61 (0.40–0.91)	0.0171	0.76 (0.48–1.18)	0.2165
Hemiplegia	0.57 (0.29–1.10)	0.0952	0.65 (0.33–1.28)	0.2150
Moderate or severe kidney disease	0.81 (0.61–1.08)	0.1549	0.85 (0.63–1.13)	0.2598
Tumor, leukemia, lymphoma	0.93 (0.72–1.19)	0.5491	1.04 (0.80–1.35)	0.7886
Moderate or severe liver disease	0.64 (0.24–1.71)	0.3700	0.63 (0.23–1.71)	0.3680
Malignant tumor, metastasis	0.42 (0.21–0.85)	0.0161	0.39 (0.19–0.82)	0.0122
AIDS				

HR: Hazard Ratio.

Another concern regarding the relationship between comorbidity and vertebral fracture also remains hotly debatable. In the literature, some reported that chronic obstructive pulmonary disease, autoimmune disease, collagen vascular disease including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren's syndrome (SS), systemic sclerosis (SSc)/mixed connective tissue disease (MCTD), polymyositis/dermatomyositis (PM/DM), and microscopic polyangiitis are related to the risk of vertebral fractures.[38–41] But those results are also related to long time steroid usage. In our study, the result showed that those connective tissue disease and chronic lung disease were not associated with repeated PVP or kyphoplasty. Our study showed that diabetes and metastatic malignant tumor were associated with repeated PVP or kyphoplasty. The reason might be that patients with diabetes have more chance to get falling down especially in the hypoglycemic status[42] and more chance to have bone destruction with metastatic malignant tumor especially involving vertebral bones. Moreover, our stratified analyses indicated diabetes and metastatic tumor could

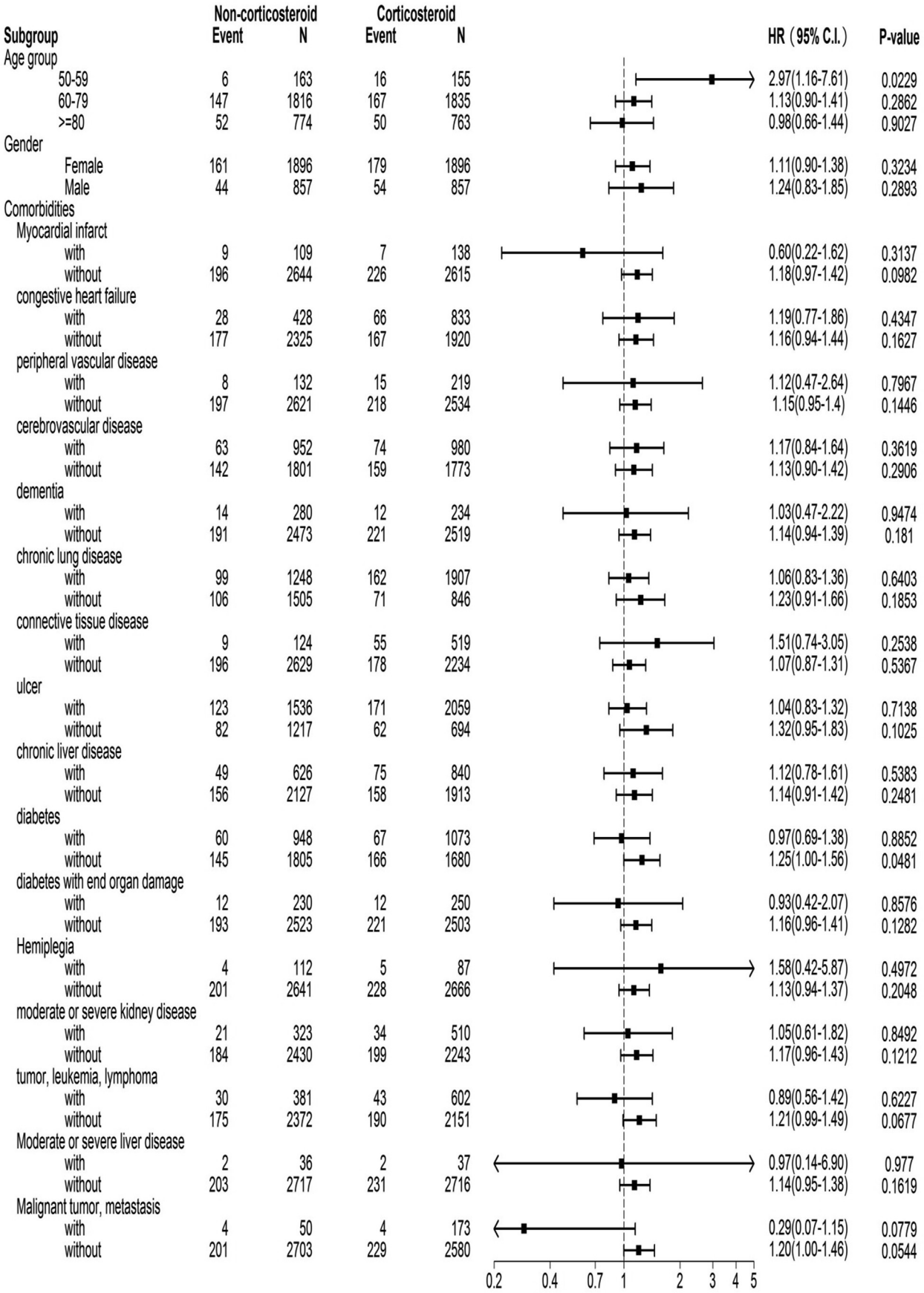

Fig. 2. Predictable risk factors for repeated vertebroplasty of kyphoplasty.

even modify the association of steroid with repeated vertebral surgery. All in all, these findings suggested these two underlying illnesses were more detrimental whether or not the patients received steroid.

Our study has some limitations. First, we could not obtain spine images. Therefore, we could not collect information regarding preoperative spine deformities, and this may have led to bias. Second, a wide range of steroid doses was used and therefore we could not determine whether differences in steroid doses would lead to different results. The follow up time in this study is only 1 year, so the finding of the study is valid for the first year after the first PVP or kyphoplasty. Nevertheless, a stringent definition of the dose would have biased the results toward a null association instead of creating a spurious one. Finally, unmeasured confounding is possible. We could not examine the potential influence of body weight, cigarette smoking, alcohol intake, and dietary habits, which are unavailable in the NHIRD. We could not acquire direct information on these factors because those external data are strictly prohibited for privacy protection. However, the merit of our study is that no loss to follow-up occurred, particularly because traveling to the hospitals covered by NHI is convenient.

In summary, the risk of receiving repeated PVP or kyphoplasty is not associated with steroid use for longer than 3 months even after the first years in patient older than 50 years old. While treating patients who have received PVP or kyphoplasty, the focus should be on treating osteoporosis.

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