Osteoporosis International (2019) 30:1043–1049
https://doi.org/10.1007/s00198-019-04863-5

ORIGINAL ARTICLE

Effect of benign prostatic hyperplasia on the development of spine, hip, and wrist fractures

S.C. Yang[1] · Y.C. Chiu[2] · P.H. Liu[3] · T.J. Hsieh[2] · Y.H. Kao[2] · Y.K. Tu[1]

Received: 2 May 2018 / Accepted: 20 January 2019 / Published online: 31 January 2019

Abstract

Summary Benign prostatic hyperplasia is one of the most common diseases in the elderly male population. The urinary tract symptoms may increase the risk of falls and fractures. The results indicated that patients with benign prostatic hyperplasia could increase the risk of vertebral compression fractures in both the thoracic and lumbar spine and also hip fractures, but did not increase the risk of wrist fracture.

Introduction The relationship between benign prostatic hyperplasia and the development of fall-related fractures, especially vertebral compression fractures, has been seldom mentioned in the literature. This study aimed to evaluate the risk of developing vertebral compression fracture, hip fracture, and wrist fracture in patients with benign prostatic hyperplasia.

Methods This study obtained claims data retrospectively from the National Health Insurance Research Database of Taiwan and identified 48,114 patients who were diagnosed as having benign prostatic hyperplasia. Subjects of the control cohort were individually matched at a ratio of 4:1 with those in the benign prostatic hyperplasia cohort according to age and the index day. Comorbidities were classified as those existing before the index day and included a previous fracture history, osteoporosis, myocardial infarction, congestive heart failure, diabetes mellitus, hypertension, cerebrovascular accident, etc. The end of the follow-up period of the analyses was the day when the patient developed new vertebral compression fractures, hip fractures, or wrist fractures, terminated enrollment from the National Health Insurance, or died or until the end of 2012. The study used the Cox proportion hazard model to determine the hazard ratio for developing new hip fractures.

Results Patients with benign prostatic hyperplasia were significantly more likely than those in the control cohort to develop new vertebral compression fractures in the thoracic spine (0.43% vs. 0.40%, adjusted hazard ratio 3.03, confidence interval 2.12–4.31) and lumbar spine (1.26% vs. 1.23%, adjusted hazard ratio 4.12, confidence interval 3.39–5.01), and hip fracture (1.47% vs. 2.09%, adjusted hazard ratio 1.22, confidence interval 1.10–1.36), but does not increase the risk of wrist fracture (0.61% vs. 0.67%, adjusted hazard ratio 1.07, confidence interval 0.85–1.34).

Conclusions Patients with benign prostatic hyperplasia exhibited an increased risk of developing vertebral compression fractures in both the thoracic and lumbar spine and also hip fractures, but did not increase the risk of wrist fracture. However, more research is needed to confirm this trend in the clinical setting.

Keywords Benign prostatic hyperplasia · National Health Insurance Research Database of Taiwan · Vertebral compression fracture

S.C. Yang and Y.C. Chiu contributed equally to this work.

✉ S.C. Yang
edaspine@gmail.com

✉ Y.C. Chiu
edatrauma@gmail.com

[1] Department of Orthopedic Surgery, E-Da Hospital / I-Shou University, No.1, E-Da Road, Kaohsiung City, Taiwan 82445, People's Republic of China

[2] Department of Orthopedic Surgery, E-Da Hospital, No.1, E-Da Road, Kaohsiung City, Taiwan 82445, People's Republic of China

[3] Department of Biomedical Engineering, I-Shou University, No.8, E-Da Road, Kaohsiung City, Taiwan 82445, People's Republic of China

Introduction

Benign prostatic hyperplasia (BPH), one of the most common benign neoplasm in elderly men, is a chronic condition associated with progressive lower urinary tract symptoms (LUTS), such as nocturia, and it affects almost three of four men during the seventh decade of life [1]. Approximately 6.5 of 27 million white men aged 50 to 79 years in the USA in 2000 were estimated to meet the criteria for discussing treatment of BPH [2].

The vertebra, hip, and wrist are the most common areas susceptible to a fracture when one has osteoporosis. The most common etiology is pre-existing osteoporosis followed by a minor trauma, such as an accidental fall [3]. These fractures represent an important cause of disability and morbidity in the elderly population, and they have a negative effect on quality of life, physical function, mental health, and survival [4]. In theory, the rate of falls may be higher in patients with BPH and result in a higher rate of vertebral compression fractures (VCFs) [5]. However, the relationship between BPH and VCFs is still unknown in the literature. In this retrospective cohort study, which derived data from the National Health Insurance Research Database (NHIRD) of Taiwan, we attempted to determine the risk of developing VCFs in patients with BPH. We also evaluate the risk between hip or wrist fractures and BPH.

Materials and methods

Source of data

The National Health Insurance (NHI) program in Taiwan has operated since 1995 and nearly all inhabitants of the country are enrolled. The NHIRD at the National Health Research Institutes (NHRI) is currently in charge of the entire database of NHI claims and published numerous extracted datasets for researchers. The NHRI released a cohort dataset composed of 1,000,000 randomly sampled people who were alive during 2000. This dataset is called the Longitudinal Health Insurance Database 2000 (LHID 2000). The database includes all the records of these individuals from 1997 to the present. Until the end of 2012, all sampled individuals were followed up for outcome identification by using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM).

The present study was exempt from full review by the local ethics review committee (IRB No. EMRP-101-027).

Subjects

This study used the LHID 2000 to investigate the risk of VCFs following the diagnosis of BPH. Patients aged more than 40 years who visited an outpatient department at least three times or were admitted to a ward once because of the diagnosis of BPH (ICD-9-CM code 600.X) from January 1, 1997, to December 31, 2010, were screened. Finally, we identified 53,793 patient diagnoses as having benign prostatic hyperplasia (the BPH cohort). The date of the initial diagnosis of BPH was defined as the index day. Subjects of the control cohort were individually matched at a ratio of 4:1 with those of the BPH cohort according to age and the index day. Comorbidities were classified as diseases, such as diabetes mellitus, hypertension, osteoporosis, liver disease, and cardiovascular disease, that existed before the index day. The end of the follow-up period of the analyses was the day that the patient developed a new closed fracture of the thoracic vertebra (ICD-9-CM code 805.2), closed fracture of the lumbar vertebra (ICD-9-CM code 805.4), closed fracture of the hip (ICD-9-CM code 820.X), or closed fracture of the wrist (ICD-9-CM code 813.4), terminated enrollment from the NHI, or died or until the end of 2012.

Statistical analysis and comorbidity risk analysis

Differences among groups were evaluated using the Student *t* test for continuous variables and the chi-square test for categorical variables. A Cox proportional hazard model was used to evaluate the risk of developing new VCFs between the BPH cohort and control cohort. The hazard ratio (HR) showed that the confidence interval (CI) was 95%. A Cox proportional hazard regression model (stratified by age group, sex, and comorbidities) was also used to estimate the risk of new VCFs. Sensitivity analyses were performed to examine whether the main findings met the various assumptions. These analyses were also performed using the Cox model on subgroups classified by age and comorbidities. The Forest plot was used to show all sensitivity analyses. All data management and calculations of HRs were conducted using Statistical Analysis System software for Windows (version 9.3; SAS Institute, Cary, NC).

Results

We reviewed 272,853 patients who were selected from Taiwan's LHID 2000 between 1997 and 2012 and divided them into the BPH cohort ($n = 22{,}965$) and control cohort ($n = 76{,}134$) (Fig. 1). The distribution of age was not different between the two groups (Table 1). All patients were followed for 15 years in the NHRI database. We identified 1050 thoracic fractures and 3492 lumbar fractures. Figures 2 and 3 show significant difference in cumulative incidence of thoracic and lumbar fractures between the benign prostatic hyperplasia patients and non-benign prostatic hyperplasia patients. Tables 2 and 3 show that patients diagnosed as having BPH had a significantly higher incidence than those in the control

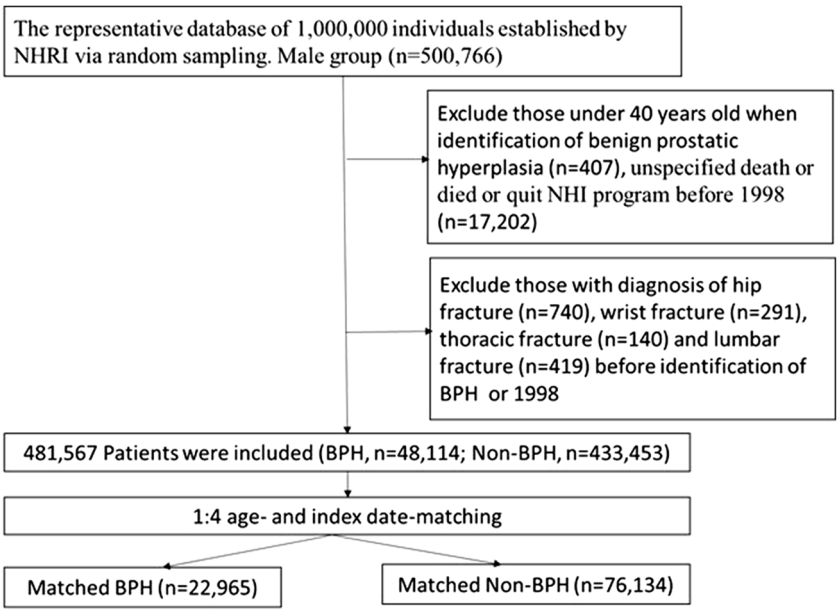

Fig. 1 The flowchart of the cohort in this study

cohort of developing new VCFs in the thoracic spine (0.43% vs. 0.40%, adjusted hazard ratio 3.03, confidence interval 2.12–4.31) and lumbar spine (1.26% vs. 1.23%, adjusted hazard ratio 4.12, confidence interval 3.39–5.01). Figure 4 shows significant difference in cumulative incidence of hip fracture between the benign prostatic hyperplasia patients and non-benign prostatic hyperplasia patients. Table 4 shows that patients diagnosed as having BPH had a significantly higher incidence than those in the control cohort of developing hip fracture (1.47% vs. 2.09%, adjusted hazard ratio 1.22, confidence interval 1.10–1.36). Figure 5 shows a significant difference in cumulative incidence of wrist fracture between the benign prostatic hyperplasia patients and non-benign prostatic hyperplasia patients. However, Table 5 shows that after matching, patients diagnosed as having BPH did not have a significantly higher incidence than those in the control cohort of developing wrist fracture (0.61% vs. 0.67%, adjusted hazard ratio 1.07, confidence interval 0.85–1.34).

Discussion

BPH is an enlarged prostate gland that develops in most men as they age. Issa et al. [6] obtained claims data from the Integrated Health Care Information Solutions National Managed Care Benchmark database (Waltham, MA) and found that BPH is the fourth most commonly diagnosed disorder in men aged 50 years or older in the USA. Chronic bladder outlet obstruction secondary to BPH may lead to various urinary problems, such as difficulty getting a urine stream started and completely stopped, weak urine stream and nocturia. Nocturia is defined by the International Continence Society when an individual awakens at night one or more times to void, which can interrupt one's sleep circle significantly [7]. Sleep fragmentation in older adults can cause serious consequences for daytime function, mood, quality of life, and health [8–10]. The average first nocturia episode occurs within 2 to 3 h of going to bed, which is usually in the phase of slow-wave sleep (SWS). Awakening in the SWS is associated with a higher risk of falls. In a previous study, falls during the nighttime among the elderly population increased from 10 to 21% with two or more voids per night [11]. Falls and associated complications are a main source of morbidity, disability, hospitalization, and mortality. In a previous study, the direct medical costs for falls were $616.5 million for fatal and $30.3 billion for non-fatal injuries in 2012, and these costs increased to $637.5 million and $31.3 billion, respectively, in 2015 [12].

A patient with the symptom of nocturia usually awakens at night several times. The disruption of sleep can result in an inattentive status while walking to the toilet, which may increase the risk of falling. BPH usually affects elderly patients, and these individuals usually experience problems of osteoporosis [13]. A 60-year-old man has an approximately 25% chance of having an osteoporotic fracture during his lifetime [14]. Although the prevalence of vertebral or hip fracture in older men is only about one-third that in women [15], the mortality rate is higher in men than in women [16, 17]. A patient with osteoporosis can develop severe complications, such as fractures, after a falling episode. Temml et al. reported a study with enrollment of 1820 men and found that the occurrence of hip fractures increased from 0.9 (no nocturia) to 1.0% (nocturia once) and to 2.7% (nocturia twice or more) [18].

De Laet et al. explored the relationship of BMI with fracture risk (any fracture, any osteoporotic fracture, and hip fracture alone) in men and women using data from 12 prospective

Table 1 Comparison of demographic and clinical characteristics of BPH and non-BPH populations

	Matched BPH ($n = 22,965$)	Matched non-BPH ($n = 76,134$)	p value
Age	61.20 ± 10.65	60.03 ± 9.87	< 0.0001
< 50	2859 (12.45)	10,223 (13.43)	< 0.0001
50 ≤ age < 65	12,438 (54.16)	43,790 (57.52)	
≧ 65	7668 (33.39)	22,121 (29.06)	
CCI	1.94 ± 2.21	0.10 ± 0.48	< 0.0001
Comorbidities			
Myocardial infarct	522 (2.27)	112 (0.15)	< 0.0001
Congestive heart failure	1357 (5.91)	189 (0.25)	< 0.0001
Peripheral vascular disease	910 (3.96)	56 (0.07)	< 0.0001
Cerebrovascular disease	3052 (13.29)	631 (0.83)	< 0.0001
Dementia	370 (1.61)	33 (0.04)	< 0.0001
Chronic lung disease	3787 (16.49)	426 (0.56)	< 0.0001
Connective tissue disease	577 (2.51)	50 (0.07)	< 0.0001
Ulcer	7070 (30.79)	951 (1.25)	< 0.0001
Chronic liver disease	4241 (18.47)	406 (0.53)	< 0.0001
Diabetes	5195 (22.62)	2899 (3.81)	< 0.0001
Diabetes with end organ damage	1232 (5.36)	131 (0.17)	< 0.0001
Hemiplegia	710 (3.09)	107 (0.14)	< 0.0001
Moderate or severe kidney disease	3631 (15.81)	393 (0.52)	< 0.0001
Malignant tumor	1780 (7.75)	258 (0.34)	< 0.0001
Leukemia	15 (0.07)	5 (0.01)	< 0.0001
Lymphoma	48 (0.21)	16 (0.02)	< 0.0001
Moderate or severe liver disease	159 (0.69)	33 (0.04)	< 0.0001
Metastasis	368 (1.6)	36 (0.05)	< 0.0001
Osteoporosis	10 (0.04)	4 (0.01)	< 0.0001

population-based cohort studies in an international perspective. The results indicated that the risk ratio (RR) per unit of higher BMI was 0.98 (95% CI, 0.97–0.99) for any fracture, 0.97 (95% CI, 0.96–0.98) for osteoporotic fracture, and 0.93 (95% CI, 0.91–0.94) for hip fracture (all $p < 0.001$). Therefore, a low BMI confers a risk of substantial importance for all fractures that is largely independent of age and sex, but dependent on BMD [19]. Therefore, the relationship between higher BMI and BPH seems to be connected to the fracture risk, evidenced by the tendency of fracture. Validation of hip

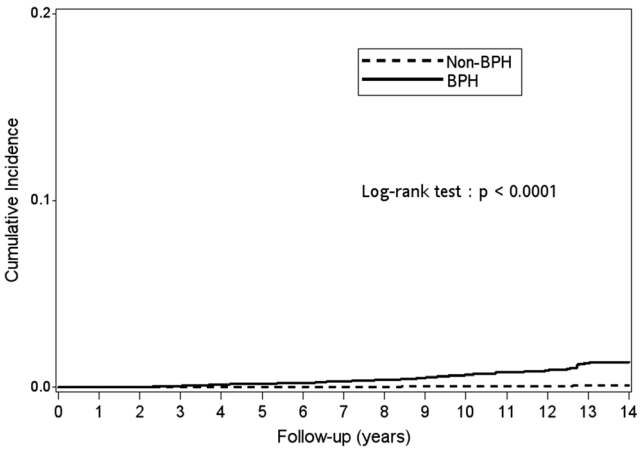

Fig. 2 Cumulative incidence of thoracic fracture between the benign prostatic hyperplasia patients and non-benign prostatic hyperplasia patients

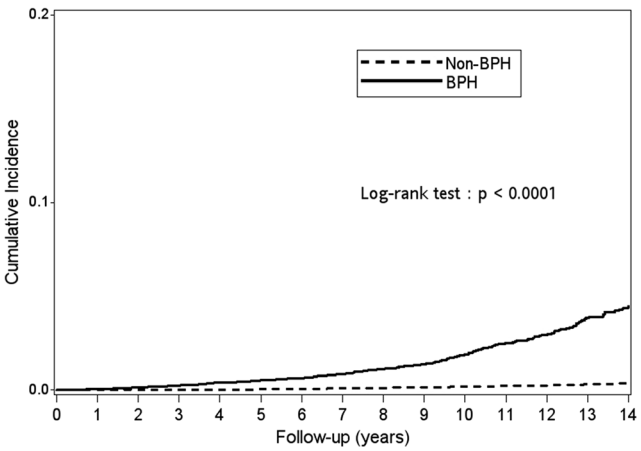

Fig. 3 Cumulative incidence of lumbar fracture between the benign prostatic hyperplasia patients and non-benign prostatic hyperplasia patients

Table 2 Analysis of incidence rate per 100,000 person-years of thoracic fracture between the benign prostatic hyperplasia patients and non-benign prostatic hyperplasia patients after matching by the Cox proportional hazard model

	No.	No. of thoracic fractures	IR (95% CI)
Age < 50			
Non-BPH	102,23	26	16.31 (10.66–23.9)
BPH	2859	7	35.41 (14.24–72.95)
50 ≤ age < 65			
Non-BPH	43,790	128	18.98 (15.84–22.57)
BPH	12,438	33	45.48 (31.31–63.87)
Age ≧ 65			
Non-BPH	22,121	176	62.55 (53.65–72.51)
BPH	7668	51	116.64 (86.85–153.36)
Overall			
Non-BPH	76,134	330	29.59 (26.49–32.97)
BPH	22,965	91	66.89 (53.85–82.12)

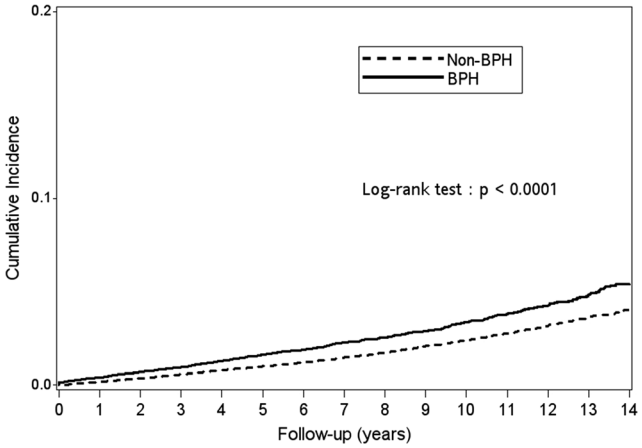

Fig. 4 Cumulative incidence of hip fracture between the benign prostatic hyperplasia patients and non-benign prostatic hyperplasia patients

fracture risk was investigated using the Rotterdam Study by De Laet et al. [20]; the result showed that the 1-year hip fracture risk estimate was calculated for each participant according to the risk function and categorized as low (< 0.1%), moderate (0.1 to < 1%), or high (≥ 1%). Moreover, above the age of 70 years, the observed incidence was high in the high-risk group; for comparison with this study, the high risk of hip fracture was evidenced in the subgroup of over 65 years old. Furthermore, a strong association between BPH and the elderly has also been confirmed by this study. The BPH effect was observed with a relation of hip fracture and able to predict hip fracture rates.

Souverein et al. [21] designed a population-based case-control study and found that BPH and LUTS were independent risk factors for a hip or femur fracture. However, the relationship between VCFs, probably one of the most devastating consequences after a fall, and BPH is still unclear. BPH-related LUTS is believed to be caused by the smooth muscle tension in the prostate stroma, urethra, and bladder neck. The symptoms of BPH usually occur easily in the elder men, particularly in those over 60 years old. The 5-alpha-reductase inhibitors (5ARIs) are the potent androgen responsible for the development and enlargement of the prostate gland by decreasing dihydrotestosterone (DHT). The 5ARIs have been associated as a high-risk factor for osteoporosis as observed by the study of Lin et al. [22]. The medication effect can be identified for osteoporosis diagnosis among patients with BPH. Parsons et al. [23] evaluated the association of LUTS with the risk of falls in elderly subjects of community-

Table 3 Analysis of incidence rate per 100,000 person-years of lumbar fracture between the benign prostatic hyperplasia patients and non-benign prostatic hyperplasia patients after matching by the Cox proportional hazard model

	No.	No. of lumbar fractures	IR (95% CI)
Age < 50			
Non-BPH	102,23	78	48.94 (38.69–61.08)
BPH	2859	18	91.05 (53.96–143.89)
50 ≤ age < 65			
Non-BPH	43,790	435	64.51 (58.59–70.86)
BPH	12,438	102	140.58 (114.63–170.66)
Age ≧ 65			
Non-BPH	22,121	447	158.87 (144.49–174.31)
BPH	7668	162	370.51 (315.65–432.17)
Overall			
Non-BPH	76,134	960	86.09 (80.73–91.72)
BPH	22,965	282	207.28 (183.79–232.94)

Table 4 Analysis of incidence rate per 100,000 person-years of hip fracture between the benign prostatic hyperplasia patients and non-benign prostatic hyperplasia patients after matching by the Cox proportional hazard model

	No.	No. of hip fractures	IR (95% CI)
Age < 50			
Non-BPH	102,23	35	21.96 (15.3–30.54)
BPH	2859	10	50.58 (24.26–93.02)
50 ≤ age < 65			
Non-BPH	43,790	297	44.04 (39.18–49.35)
BPH	12,438	103	141.96 (115.87–172.17)
Age ≧ 65			
Non-BPH	22,121	790	280.78 (261.54–301.07)
BPH	7668	367	839.37 (755.68–929.8)
Overall			
Non-BPH	76,134	1122	100.62 (94.82–106.69)
BPH	22,965	480	352.81 (321.95–385.83)

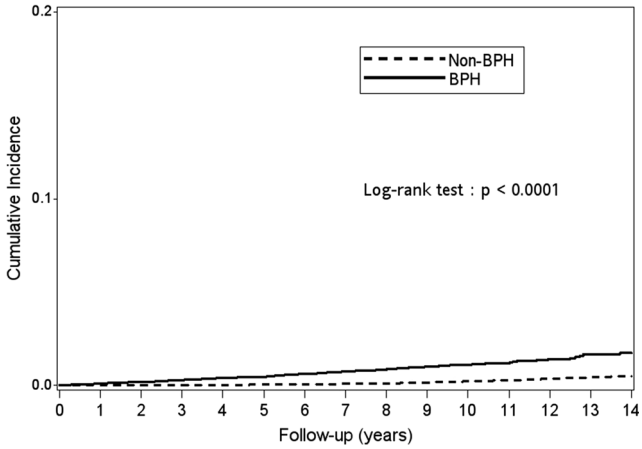

Fig. 5 Cumulative incidence of wrist fracture between the benign prostatic hyperplasia patients and non-benign prostatic hyperplasia patients

dwelling men, aged ≥ 65 years, with baseline osteoporotic fractures. The results showed that the risk of at least one fall was increased by 11% among those with moderate and by 33% among those with severe LUTS. Furthermore, the LUTS most strongly associated with falls were urinary urgency, difficulty initiating urination, and nocturia. On the other hand, BPH has been confirmed to influence directly LUTS. Therefore, the same tendency of fracture risk is identified due to LUST and BPH when a previous Parsons's study and our research are compared.

There are several options for the management of distal radius fracture in the aging population. However, current evidences suggest non-surgical treatment is a valid method with similar results to surgical intervention. Even highly active elderly patients do well with non-surgical management [24, 25]. Some patients in Taiwan with distal radius fracture may even receive conservative treatment by traditional Chinese medicine or a bonesetter that will not be shown in this database. Therefore, different from spine or hip fracture, this will make us underestimate the effect of BPH on the development of distal radius fracture and also present as non-significantly different the development of wrist fracture in this study.

In our study, the risk of developing new VCFs in the thoracic and lumbar spine was significantly higher in patients who were diagnosed as having BPH previously than in the control cohort. The increasing risk may be caused by a higher falling incidence related to the side effect of treatment or the disease itself. Taking into consideration the severe complications after falling, such as a hip or vertebral fracture, physicians should try to prevent patients from falling by treating patients with BPH. Comprehensive health education, adequate use of medications to prevent side effects, and improvement of the patient's home environment can decrease the fall-related complications.

The diagnosis of relationship between bone fracture and osteoporosis is an important issue to obtain an accurate incidence of osteoporotic-induced fractures in the different fracture sites. Hence, Delmas et al. [26] indicated that accurate radiographic diagnosis for evaluating vertebral fractures is an important method to obtain a relationship between a patient's fracture and osteoporosis. We believe that vertebral fractures are the most common complications of osteoporosis. Moreover, Gehlbach et al. [27] also pointed out that osteoporosis-related vertebral fractures have important health consequences for older individuals who are high-risk patients. The relationship between vertebral fractures and osteoporosis is identified by radiographic evidence.

To the best of our knowledge, this study is the first to discuss the relationship between BPH and new-onset VCFs. The strength of this study was the uniform data collection in a well-defined population. However, there were several limitations worth highlighting. First, the insurance data set does not provide detailed information on physical activity, economic status, and patient compliance, which are all potentially confounding factors relevant to the development of subsequent VCFs. Second, the severity and treatment methods of BPH could not be determined in the data set. Third, a retrospective cohort study design is subject to biases related to confounding adjustments. Despite using a carefully designed study with adequate controls, bias might have remained because of unmeasured or unknown confounders. Fourth, some VCFs may not be presented in the database because of missed coding by physicians or the patients were asymptomatic, which may further increase the bias in this study. Additional longitudinal studies are necessary to validate the relationship between BPH and newly developed VCFs.

Table 5 Analysis of incidence rate per 100,000 person-years of wrist fracture between the benign prostatic hyperplasia patients and non-benign prostatic hyperplasia patients after matching by the Cox proportional hazard model

	No.	No. of wrist fractures	IR (95% CI)
Age < 50			
Non-BPH	102,23	65	40.79 (31.48–51.99)
BPH	2859	26	131.51 (85.91–192.69)
50 ≤ age < 65			
Non-BPH	43,790	256	37.96 (33.45–42.91)
BPH	12,438	65	89.59 (69.14–114.19)
Age ≧ 65			
Non-BPH	22,121	145	51.54 (43.49–60.64)
BPH	7668	62	141.8 (108.72–181.78)
Overall			
Non-BPH	76,134	466	41.79 (38.08–45.76)
BPH	22,965	153	112.46 (95.35–131.76)

Conclusions

The results of this retrospective cohort study indicate that the risk of new VCFs and hip fractures increased significantly in patients with BPH. Physicians should keep in mind that preventing falls and their related consequences is valuable in treating patients with BPH.

Acknowledgements We would like to thank the Center for Database Research, E-DA Hospital, and Intelligent Medical Big Data Co., Ltd. for data analysis and the Research Database (National Health Insurance Research Database 103-116) by the National Health Insurance.

Funding information This work was also supported by the Room for Database Research, E-Da Healthcare Group, in the acquisition of data (CFDR-B-104-3-2, CFDR-B-104-3-3, and EDAD 10703).

Compliance with ethical standards

The present study was exempt from full review by the local ethics review committee (IRB No. EMRP-101-027).

Conflicts of interest None.

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