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ORIGINAL ARTICLE

Re-fracture and correlated risk factors in patients with osteoporotic vertebral fractures

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Abstract

Re-fracture risk is higher following osteoporotic fracture. However, there is no accurately reported rate of re-fracture incidence in southwest China. The purpose of this study was to describe the osteoporotic vertebral fracture (OVF) survival for re-fracture state and analyze the risk of re-fracture. This historical cohort study was conducted in four hospitals in southwest China. Patients aged ≥ 50 years ($n = 586$) with OVF who were supposed to receive anti-osteoporosis drugs after the fracture were included (2012–2017). Telephone follow-up and referring case files were used to estimate the survival for re-fracture and identify the determinants of re-fracture. A total of 555 patients completed the follow-up investigation. Overall, 285 patients experienced a re-fracture, and the longest follow-up investigation time was 72 months. The survival rates for re-fracture at 12 months, 24 months, 36 months, and 48 months were 82.0%, 71.5%, 61.7%, and 34.0%, respectively. The factors correlated with re-fracture hazard were advanced age [hazard ratio (HR) = 1.996], being female (HR = 1.342), smoking (HR = 1.435), history of hypertension (HR = 1.219) and diabetes (HR = 3.271), and persistence of taking anti-osteoporosis drugs after fracture [0–3 months, 4–6 months, 7–12 months, and more than 12 months (HR = 0.703)]. OVF patients with advanced age, who were female, smoked, had fracture with hypertension or diabetes, and who complied poorly with anti-osteoporosis drug treatment presented higher prevalence of re-fracture and low anti-osteoporosis adherence in southwest China. The management of anti-osteoporosis after fracture is necessary in this area.

Keywords Osteoporotic vertebral fracture · Re-fracture · Osteoporosis · Anti-osteoporosis

Introduction

With the acceleration of population aging in China, osteoporotic fractures (OPF) are becoming a threat to the health of older adults. Such fractures are characterized by poor bone strength, a complicated fracture healing process, and a high incidence of re-fracture. The greatest number of men and women at high risk are from Asia (55%) and, worldwide, the number of high-risk individuals is expected to double over the next 40 years [1]. The increasing importance of preventive measures in the field of orthopedics and trauma surgery becomes apparent in view of the demographic changes and the high risk of secondary fractures following OPF. Prior fractures are strong predictors of another fracture risk. Indeed, the risk of another fracture is twofold higher following a non-vertebral fracture and quadruples after a vertebral fracture; women who develop a vertebral fracture are at substantial risk of additional fracture within the next year [2]. This risk is not constant over time but increases to a fivefold higher risk in the year after the first fracture, followed by a gradual waning [3]. Within 5 years after the initial fracture, up to one-third of such patients will sustain a new fracture [4].

Through the follow-up of 586 patients from four hospitals in southwest China, this study describes osteoporotic vertebral fracture (OVF) patients' survival for re-fracture and some protective factors against potential risks. Thus far, to the best of our knowledge, this is the largest sample and longest follow-up study of OVF patients' prognosis

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in southwest China, which compensates for the lack of re-fracture-related research in this area. We hope this study can provide some references for prognostic prospects and post-fracture management.

Material and methods

Study design

This historical cohort study was conducted using clinical and medical record data. All patients who underwent fracture treatment in four hospitals in southwest China between 2012 and 2017 were followed through medical record data and via telephone to examine the occurrence of re-fracture. The follow-up period began from the day of the initial fracture to re-fracture, lost to follow-up, or up to the follow-up censored time.

Participants

From January 1, 2012, to December 31, 2017, patients with OVF who were hospitalized in the orthopedic departments of four hospitals located in southwest China and who met the following criteria were included. Inclusion criteria were as follows: (1) patients who met the diagnostic criteria of OPF as defined by clinical guidelines; (2) patients who suffered a first fracture and were over 50 years old; (3) patients who had lived in southwest China (at a fixed address) for more than 10 years and resided legally in this area continuously for not less than 10 months annually; (4) patients who were supposed to continue anti-osteoporosis treatment with doctor's advice, and (5) fracture sites in the vertebral column. Exclusion criteria included: (1) patients with diseases that interfere seriously with bone metabolism (including Cushing's disease, hyperthyroidism, hyperparathyroidism, thyroid cysts, or hypothyroidism) and/or fractures due to bone tumors or bone tuberculosis caused by pathological fractures and (2) fractures caused by serious violence. A total of 593 patients met these criteria and formed this study's follow-up cohort.

Data collection

Patient demographics, history, and treatment were collected using the case report form survival for re-fracture of OPF patients and risk factors related to re-fracture questionnaire. According to the common risk factors of re-fracture in patients with OVF, reported at home and abroad, combined with items recorded in the medical records, a total of nine indicators were included as follows: age, gender, smoking, history (hypertension and/or diabetes), conservative or surgical treatment, hospitalization days, and time of persistence with anti-osteoporosis drugs after fracture. Data were collected via telephone follow-up and referring case files.

Clinically evaluated criteria and factor definition

This study defines smoking as the continuous daily consumption of ≥ 3 cigarettes or ≥ 18 cigarettes per week for more than one year; patient history focused on hypertension and diabetes that met the international standard diagnostic criteria. According to the pilot survey reference, the time of persistence with anti-osteoporosis drugs after fracture was divided into four groups: 0–3 months, 4–6 months, 7–12 months, and more than 12 months. The medication possession ratio (MPR) was used to evaluate the persistence with anti-osteoporosis medication [5]. Patients with MPR > 80% were considered to be well compliant and their duration of drug use was included in the analysis [6]. Both initial fracture and re-fracture OVF referred to fractures that occur in everyday life without apparent external force or by the body's force from standing or falling below standing height, which were assessed according to the latest guidelines for the diagnosis and treatment of OPF [7].

Follow-up survey

The follow-up content: (1) further verified the patients' medical history, personal history, onset time, and smoking status; and (2) elucidated the duration of the patients' medication after discharge and survival for re-fracture and whether they had experienced re-fracture or died from re-fracture and the accurate time to death (d). This study ended on December 31, 2017.

Statistical analysis

Kolmogorov–Smirnov tests were performed on continuous variables, respectively, and the variables fitted with normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$). Counting data were expressed in terms of frequency and percentage. Log-rank tests were used to test for significant differences between groups. Kaplan–Meier survival analysis was initially performed on all of the patients, followed by univariate Cox analysis of each variable; variables that had statistically significant differences were entered in the multivariate Cox analysis. Multi-category variables entered the regression model as dummy variables. Variables candidate standard $\alpha \leq 0.10$.

Results

Baseline and follow-up survey

By the end of the censoring time, 285 patients experienced re-fracture (243 vertebral fracture, 16 hip fracture,

11 proximal humerus fracture, 8 distal radius fracture, 7 others). The incidence of non-surgical vertebral fractures was 40.33% (98/243), of which adjacent vertebral fractures accounted for 65.31% (64/98). The longest follow-up period was 72 months. Thirty-one (5.29%) patients were lost to follow-up and 8 died from causes unrelated to re-fracture (3 died of cerebrovascular accident, 2 died of lung infection, 1 died in a traffic accident, 1 died of myocardial infarction, and 1 died of foreign bodies in the esophagus). No statistical differences were observed in baselines data between the lost-group patients and the retained-group patients ($P > 0.05$). The average follow-up time was 36.31 ± 14.68 months, and the median survival time for another fracture was 36 months. The differences in survival for re-fracture time, smoking history, hypertension, diabetes, time of persistence with anti-osteoporosis drugs after fracture, and treatment in the two groups were statistically significant ($P < 0.05$) (Table 1). Survival analysis using Kaplan–Meier showed that the survival rates for re-fracture of 6 months, 12 months, 24 months, 36 months, and 48 months were 94.8%, 82.0%, 71.5%, 61.7%, and 34.0%, respectively.

Univariate Cox analysis

All variables were introduced into the Cox model for univariate analysis. Treatment (conservative as reference), history (none as reference), time of persistence with anti-osteoporosis drugs after fracture (more than 12 months as reference), and smoking status met the study's statistical significance (P value less than the rejection criterion of 0.11) (Table 2).

Multivariate Cox regression analysis

Five factors that had statistically significant differences in univariate analysis were gradually introduced into a Cox proportional hazards model for multivariate analysis with the forward condition method. According to the size of the HR, the top three factors that greatly affected the outcome variables were the following: history of diabetes, age, and smoking status. Further, insistence on using anti-osteoporosis drugs after fracture was a protective factor against re-fracture (Table 3).

Table 1 Baseline data for re-fracture and no re-fracture groups ($n = 555$)

	Re-fracture ($n = 285$)	No re-fracture ($n = 270$)	t/χ^2	P
Age (years)	66.26 ± 7.901	67.33 ± 9.544	0.812	0.417
Gender (male/female)	92/193	102/168	5.873	0.015
Hospitalization (days)	12.88 ± 9.776	12.72 ± 7.837	0.208	0.835
Survival time (months)	21.17 ± 14.68	35.45 ± 13.658	10.824	< 0.001
Smoking (yes/no)	120/165	90/180	4.536	0.033
History				
Diabetes	25	5	7.284	0.007
Hypertension	52	41		
Anti-osteoporosis				
0–3 months	232	178	22.987	< 0.001
4–6 months	47	65		
7–12 months	5	22		
> 12 months	1	5		
Treatment (surgical/conservative)	252/33	252/18	4.009	0.045

Table 2 Univariate Cox analysis associated with re-fracture in patients with OVF

	B	SE	P value	HR	95% CI	
Gender	0.415	0.206	0.044	1.514	1.012	2.265
Age	− 0.016	0.007	0.028	1.984	1.971	1.998
Hospitalization	0.001	0.008	0.889	1.001	0.986	1.016
Treatment	− 0.416	0.164	0.011	0.659	0.478	0.909
History			< 0.001			
Hypertension	0.313	0.153	0.041	1.368	1.013	1.847
Diabetes	0.932	0.321	0.004	2.539	1.353	4.767
Anti-osteoporosis	− 0.337	0.117	0.004	0.714	0.567	0.898
Smoking	0.337	0.128	0.009	1.401	1.090	1.802

Table 3 Multivariate Cox analysis associated with re-fracture in patients with OVF

	B	SE	*P* value	HR	95% CI	
Treatment	− 0.199	0.039	< 0.001	0.819	0.759	0.884
History			< 0.001			
Hypertension	0.198	0.033	< 0.001	1.219	1.142	1.302
Diabetes	1.185	0424	0.005	3.271	0.845	3.548
Anti-osteoporosis	− 0.353	0.117	0.003	0.703	0.559	0.883
Smoking	0.361	0.128	0.005	1.435	1.118	1.843
Age	− 0.004	0.002	0.014	1.996	1.993	1.999
Gender	0.294	0.048	< 0.001	1.342	1.223	1.473

Discussion

Re-fracture

As shown in this study, during the follow-up of 72 months, 51.35% of the patients experienced re-fracture, and the survival rates for re-fracture at 12 months, 36 months, and 48 months were 82.0%, 61.7%, and 34.0%, respectively. Previous research found that a patient with OPF risked a secondary fracture probability 2–9 times higher than the non-osteoporotic person [8]. In a statewide analysis of hospital admission data from New South Wales, Australia, 35% of patients with incident OPF suffered re-fracture within 6 years [9]. In another study, during a mean follow-up of 5.2 years, 26.3% of all subjects re-fractured [10]. A 4-year prospective controlled study in the United States found that 19.7% of patients suffered a new fracture [11]. A 2-year follow-up re-fracture rate of 15.20% was reported in northwest China [12]. By comparison, the re-fracture rate in this study was significantly higher than previously reported. The most possible explanation is that the subjects mentioned in references [6–10] were different. Reference [6] focused on the absolute risk of subsequent fracture following initial low-trauma fracture, and other research assessed all types of OPF, including non-vertebral OPF and vertebral fracture. Among them, OVF was usually associated with much lower bone mineral density (BMD). In addition, the OVF patients' activities were limited much more seriously than the other patients', and decreased mobility could further exacerbate bone loss. The participants in this research consisted of ethnic minorities in southwestern China, an underdeveloped area where most ethnic minorities have diverse lifestyles. The economic and demographic characteristics are different from those in developed regions. This indicates the necessity of understanding the prognosis of OVF in this area and improving post-fracture management.

Related factors (risk factors)

Hypertension and diabetes are common in the elderly. Previous studies showed that the prevalence of re-fracture in OPF patients with a history of diabetes was 2.247 times as much as in patients without diabetes [13]. We found a higher rate in this research (HR = 3.271, 95% CI 0.845–3.548, $P < 0.001$). Because of hyperglycemia, lack of insulin secretion and diabetic complications such as diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy can cause changes in bone metabolism. Further, fracture may prolong bed rest, pain, surgical trauma, and other stress factors, which also exert a negative effect on blood glucose control. Overall, hyperglycemia can induce systemic metabolic disorders and will exacerbate bone metabolism and osteoporosis, increasing the re-fracture rate. Therefore, diabetes is undoubtedly an independent risk factor for re-fracture.

It was suggested that hypertension can reduce the BMD of the human body, and the degree of reduction varies in different parts of the bone. In addition, the reduction level of BMD is inconsistent in different regions and populations [14]. A meta-analysis of hypertension and OPF risk encompassing 28 independent studies, 1,430,431 participants, and 148,048 OPF cases also showed that the risk of OPF among those with hypertension was higher (HR = 1.33, 95% CI 1.25–1.40, $P < 0.001$) than that among those without hypertension [15]. In addition, high blood pressure in patients with hypertension often increases the risk of cardiovascular and cerebrovascular diseases, cardiovascular accidents, and the risk of falls and then re-fractures; therefore, hypertension is an independent OPF risk factor. We also confirmed that a history of hypertension increases the risk of re-fractures in initial OVF patients (HR = 1.219, 95% CI 1.142–1.302, $P < 0.001$).

Smoking is one of several lifestyle factors associated with increased fracture risk [16]. An association with lower BMD and increased risk of OPF in a dose- and duration-related manner has been implicated [17]. We found that smoking is an independent risk factor for OVF re-fracture (HR = 1.435, 95% CI 1.118–1.843, $P = 0.005$). It has been proven that environmental and genetic factors as well as living habits including smoking have an impact on OPF [18]. The natural environment, climate, and especially the lifestyle of southwest China differ from other areas of China. Nearly 40 nationalities live in this ethnically diverse area. Many

minorities such as Yao and Miao nationalities, especially women, tend to smoke more than other nationalities in most areas of China, and this aggravates osteoporosis [19, 20]. In addition, smoking is thought to cause an increase in the rate of perioperative complications, including soft-tissue complications, decreasing the rate of fracture union and prolonging healing time. Smoking significantly increased the risk of non-union of fractures overall, and in open fractures. Postoperative rates of superficial and deep infections were noted in smokers compared to non-smokers [21]. Smoking cessation should be recommended to OVF patients who smoke to prevent re-fracture.

Our previous study showed that age correlated negatively with BMD in the population of southwest China [22]. Indeed, aging is unanimously considered the main risk factor for OPF, as confirmed by our study. Every increase in 1 year of age increases re-fracture incidence by 1.996. Thus, elderly patients should be monitored during initial OVF treatment to prevent further fracture. In addition, epidemiologic and clinical studies have demonstrated significant differences between males and females regarding the prevalence of osteoporosis and fracture risk. It was reported that in the 27 countries of the European Union in 2010, 22 million women and 5.5 million men were estimated to have osteoporosis; notably, the number of women with new osteoporosis was four times that of men [23]. Older women are more prone to osteoporosis and fracture due to the reduction in estrogen secretion caused by menopause. Post-menopausal women with OPF had higher plasma dipeptidyl-peptidase 4 (DPP4) levels than pre-menopausal women. Furthermore, higher plasma DPP4 levels were significantly associated with greater bone turnover and an increased prevalence of OPF [24]. From menopause onward, clinical fractures cluster in time; of all first fractures, 4% occurred in each year from menopause onward, while after a first fracture, 23% of all subsequent fractures occurred within 1 year and 54% within 5 years [25]. This indicates the need for early action to prevent subsequent fractures.

In this study, patients who presented with an OVF on imaging, with correlating mild clinical signs and symptoms, as well as those who could not tolerate surgery were treated with calcitonin, ibandronate, strontium ranelate, bed rest, and complementary or alternative medicine. Although some of these remedies were not recommended, they were still popular in southwest China [26, 27]. All these treatments were collectively referred to as conservative treatments. Surgery included percutaneous vertebroplasty (PVP) or percutaneous kyphoplasty (PKP). The indication of operation were as follows: (1) unstable fracture, such as vertebral compression exceeds 1/2 of vertebral thickness, comminuted, or fracture with dislocation or ligament tear; (2) no neurological damage; (3) fresh compression fracture in spinal chest lumbar region; (4) severe kyphosis with fracture-induced refractory low back pain which resulted of spinal compression fracture; (5) upper and lower adjacent vertebrae multi-segment compression fracture which secondary to OVF. With conservative treatment as reference, patients with surgical treatment had a lower risk of re-fracture (HR = 0.819, 95% CI 0.759–0.884, $P < 0.001$). It is worth noting that more than 90% of all patients in this study underwent surgery (the ratio of PVP/PKP was 184/68 in the re-fracture group and 176/76 in the non-re-fracture group). We further investigated the patients' treatment preferences. Most chose surgical treatment mainly because it can alleviate pain and because of an orthopedist's advice. The choice of PVP or PKP mainly depended on the patients' financial means. In southwest China, the residents' income was lower than the national average, and PVP is much less expensive than PKP. Another reason may be that surgery for OPF has been implemented in southwest China since 2012. Based on the guidelines for the medical insurance reimbursement policy in the region, orthopedists may be more inclined to recommend it.

Related factors (protective factors)

Although anti-osteoporosis treatment was recommended in previous research [27], the adherence was poor in this study. A population-based cohort analysis in Spanish showed that among 95,057 patients with new anti-osteoporosis medications, the 1-year cessation rate was 51% (28–68%), higher in men, smokers, patients with missing lifestyle data, and those with abnormal BMI. It was lower in those aged 60–79 with recent fractures [28]. A study of long-term persistence with anti-osteoporosis drugs after fracture in the Dutch showed that persistence was 75.0% and 45.3% after 1 and 5 years, respectively. We found a much lower persistence rate in southwest China. As shown, only 1 patient continued anti-osteoporosis treatment for more than 12 months in the re-fracture group of 285 patients, and 4 of 197 patients in the no re-fracture group. Most patients (82.69%) stopped taking anti-osteoporosis medicine within 0–3 months in the re-fracture group, and 64.97% in the no re-fracture group, resulting in a higher rate of re-fracture. This indicates the urgency of managing long-term persistence with anti-osteoporosis drugs after fracture in this area.

It is believed that rheumatoid arthritis, hyperthyroidism, COPD, and other comorbidities are common risk factors for fractures. Diseases such as rheumatoid arthritis and hyperthyroidism that interfere with bone metabolism were excluded from this study. In other words, the results of this study are not applicable to OPF patients with these comorbidities. Although we attempted to collect possible risk factors as much as possible in multiple centers, we can only listed hypertension and diabetes and omitted others, and it also was the limitation of historical cohort study. Since this

was a historical retrospective study, the observational indicators included depended on the medical records of the original data. Some were risk factors but were not recorded in the original medical records; therefore, they were not included in the analysis. Further research should design a prospective cohort study to elucidate the greatest risk factors and provide suggestions for the prevention of re-fracture.

In conclusion OVF patients with advanced age, smoking, and fracture with hypertension or diabetes and those with poor adherence to anti-osteoporosis drug therapy have higher risks of re-fracture compared to other areas of China and worldwide as reported in previous research, OVF patients presented higher prevalence of re-fracture and lower anti-osteoporosis therapy adherence in southwest China.

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Compliance with ethical standards

Conflict of interest No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject(s) of this article.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments and/or comparable ethical standards.

Informed consent Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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