Orthopaedic Surgical Intervention and Type I Osteoporosis Are Risk Factors For Acute Febrile Reaction After Zoledronic Acid Treatment For Osteoporosis: A Case-Control Study

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Abstract

Background

Acute febrile reaction often occurs though zoledronic acid is a widely used first-line drug for osteoporosis. This study aimed to investigate the characteristics and risk factors of acute febrile reaction after zoledronic acid in the orthopaedic field, including surgical intervention.

Methods

a total of 517 patients diagnosed with primary osteoporosis and treated with zoledronic acid from January 2012 to December 2020 were collected, including 40 males and 477 females, 262 patients with type I, 255 patients with type II, 230 patients with fresh fracture, and 209 patients with the operation. Summarize the characteristics of overall fever rate, fever degree, occurrence time, and duration of the acute febrile reaction. The effects of gender, white blood cell, neutrophil, lymphocyte, neutrophil-lymphocyte ratio (NLR), type of osteoporosis, degree of osteoporosis, fresh fracture, operation, and zoledronic acid medication history on acute febrile reaction were analyzed by univariate, logistic regression, ROC curve analysis. The differences in fever rate in different fracture operation sites were further compared.

Results

In 517 patients, 175 cases (33.85%) developed acute febrile reaction within 36h after medication with less than 60h duration. Univariate analysis showed significant differences in NLR, type and degree of osteoporosis, fresh fracture, operation, and zoledronic acid history between the fever and non-fever groups ($P < 0.05$). Logistic regression and ROC curve analysis further showed that the fever rate of patients with the operation was higher ($OR = 1.975$, $P < 0.01$, area under ROC curve was 0.654). The fever rate of patients with type I osteoporosis was higher ($OR = 2.137$, $P < 0.01$, area under ROC curve was 0.437), and the fever rate of patients with zoledronic acid history was lower ($OR = 0.124$, $P < 0.01$, area under ROC curve was 0.340). The fever rate of joint fracture patients (56.60%) was significantly higher than that of spine fracture patients (38.54%) ($P < 0.05$).

Conclusion

When zoledronic acid was used to treat primary osteoporosis in orthopaedic patients, the rate of acute febrile reaction was 33.85%, orthopaedic surgical intervention, type I osteoporosis, and the first zoledronic acid treatment might be independent risk factors.

Introduction

Osteoporosis (OP) is a systemic bone disease characterized by decreased bone mass, damage of bone microstructure, increased fragility, and fracture prone[1]. Over the past 10 years, the number of osteoporosis patients in China has increased significantly. Osteoporotic fracture seriously endangers the

health and quality of life of middle-aged and older people. Surgery combined with anti-osteoporosis treatment has become a recognized new principle of fracture treatment in this field. Bisphosphonate family is the first-line drug recommended by domestic and foreign guidelines, among which zoledronic acid, as the third generation representative product, can strongly inhibit bone resorption and reduce the incidence of osteoporotic fracture[2]. Clinical observation for many years has confirmed the curative effect. However, acute-phase reaction (APR), especially fever, often occurs after medication. It greatly affects clinical treatment and patient compliance. For OP patients who need surgery, how to choose the right time of administration has been a problem for orthopaedics doctors. This study retrospectively analyzed the characteristics and influencing factors of acute febrile reaction in the zoledronic acid treatment of primary osteoporosis to provide reference and a basis for clinical diagnosis and treatment.

Materials And Methods

Ethics statement

The Medical Ethics Committee of China Medical University Affiliated Shengjing Hospital approved this study(Ethics application number: 2021PS724K) and waived the need for informed consent in the study. All clinical and laboratory variables included in this analysis were retrospectively collected. All the diagnosis and treatment methods mentioned in this paper are routine diagnosis and treatment methods. The routine diagnosis and treatment methods of patients did not change for the study. Patient records/information were anonymized before analysis, and all methods were carried out following relevant guidelines and regulations. Our research was performed under the Declaration of Helsinki.

Subjects

Collect the clinical data of patients diagnosed with primary osteoporosis (type I: postmenopausal osteoporosis, type II: senile osteoporosis) in China Medical University Affiliated Shengjing Hospital from January 2012 to December 2020. According to the WHO diagnostic criteria for osteoporosis[3], those who meet one of the following three criteria can be diagnosed as primary osteoporosis: ① brittle fracture of the hip or vertebral body; ② T value of bone mineral density of axial bone or distal 1 / 3 of radius bone measured by dual-energy X-ray absorptiometry is less than - 2.5; ③ Bone mineral density: - 2.5 ④ t value ④ - 1.0, accompanied by brittle fractures of the proximal humerus, pelvis or distal forearm. Diagnostic criteria for severe osteoporosis: ① t value of bone mineral density measured by dual-energy X-ray absorptiometry $\leq$ - 3.5. ② The degree of bone mineral density reduction was following the diagnostic criteria of osteoporosis. At the same time, one or more brittle fractures were considered severe osteoporosis, *i.e.*, t value $\leq$ - 2.5 + brittle fracture. Inclusion criteria: ① type I and type II patients who met the WHO diagnostic criteria for osteoporosis; ② The case data were recorded in detail; ③ The temperature of patients before and after treatment was recorded entirely; ④ $50 \leq \text{age} \leq 89$. Exclusion criteria: ① patients with secondary and idiopathic osteoporosis, and other metabolic bone diseases other than osteoporosis; The patients had a fever before zoledronic acid treatment; ② Patients with vitamin D deficiency; The concentration of serum calcium was less than 2.13 mmol / L; ③ Patients with renal insufficiency and serum creatinine clearance

rate less than 35 ml/min; ☒ Bacterial and viral infection occurred within one month, and immunosuppressants and glucocorticoids were used; ☒ Zoledronic acid injection allergy.

Treatment methods

All patients were given a zoledronic acid injection by intravenous drip. The infusion tube maintained a constant rate of infusion, 20-30 drops per minute, and the infusion time was 30-60min. Before and after administration, 500-1000ml normal saline injection was given by intravenous drip for complete hydration.

Observation indexes

The included patients underwent blood routine tests, liver and kidney function (and the creatinine clearance rate was calculated), blood phosphorus, blood calcium, electrocardiogram, and other tests, and no apparent abnormalities were found. Recorded the number of patients with fever and recorded the fever temperature of each patient, the beginning time, and duration of fever. Body temperature $\geq 37^{\circ}\text{C}$ is fever, $37^{\circ}\text{C} \sim 38^{\circ}\text{C}$ is low fever, $38^{\circ}\text{C} \sim 39^{\circ}\text{C}$ is moderate fever, and $\geq 39^{\circ}\text{C}$ is high fever. The correlation between acute febrile reaction and gender, leukocyte, neutrophil, lymphocyte, neutrophil-lymphocyte ratio (NLR), type of osteoporosis, degree of osteoporosis, fresh fracture, and surgery operation were analyzed.

Statistical Methods

Use Excel software to collect data to describe the overall situation. SPSS 25.0 statistical software was used for statistical analysis. The measurement data of normal distribution were expressed in mean $\pm$ standard deviation ($\bar{x} \pm s$). A single-factor chi-square test was used to study the influence of categorical count data on dependent variables. Multivariate logistic regression analysis was used for multivariate analysis. ROC curve was used to analyze the factors with a significant difference. When $p < 0.05$, the difference was statistically significant. Using GraphPad Prism 8.0 drawing software to draw.

Results

Clinical data of patients

Among the 517 patients who met the inclusion criteria, there were 40 males and 477 females, with an average age of (68.69 ± 9.19) years and an average BMD of (-3.18 ± 0.92) . 262 patients with type I OP and 255 patients with type II OP; 230 patients with fresh fracture; 245 patients with mild and moderate OP, 272 patients with severe OP; 209 patients received surgical treatment and 308 patients received non-surgical treatment. 381 patients were given zoledronic acid for the first time, and 136 patients had a history of zoledronic acid use.

Characteristics of acute febrile reaction induced by zoledronic acid

In this study, among 517 patients, 175 patients developed acute febrile reaction, the fever rate was 33.85%, the average fever temperature was $(38.15 \pm 0.74)^{\circ}\text{C}$, low fever 59 cases (37.58%), moderate fever

73 cases (46.50%), high fever 25 cases (15.92%). The mean time of febrile reaction was (16.08±15.08) h, and it occurred in 236 cases (45.65%) between 0 and 12h, 269 cases (52.03%) between 12 and 36h, and 12 cases (2.32%) over 36h after administration. The average duration of fever was (29.54±21.65) h. The duration between 0 and 12h was 133 cases (25.73%), between 12 and 36h 206 cases (39.85%), between 36 and 60h 137 cases (26.50%), and over 60h 41 cases (7.93%). (figure 1)

A: Distribution of fever degree; B: Occurrence time; C: Duration

Figure 1. **Distribution of fever degree, Occurrence time, and Duration of acute febrile response to zoledronic acid treatment in primary osteoporosis**

Univariate analysis of various influencing factors on acute febrile reaction induced by zoledronic acid

The statistical method of t-test showed no significant differences in the number of white blood cells, neutrophils, and lymphocytes before administration between patients in the febrile group and those without fever group ($P > 0.05$). However, the mean NLR of patients in the febrile group was higher than that in the non-febrile group, and the difference between the two groups was statistically significant ($P < 0.05$). See Table 1.

Table 1
Effect of premedication inflammatory markers on zoledronic acid-induced acute febrile reaction

factors	Fever group	No fever group	T value	P-value
WBC	6.58±2.58	6.13±2.18	1.887	0.06
neutrophils	4.36±2.49	3.92±2.04	1.954	0.052
The lymphocyte	1.6±0.59	1.62±0.60	-0.466	0.641
NLR	3.67±4.40	2.94±2.54	2.025	0.044

Statistical analysis by chi-square test showed that the fever rate of patients with type I OP was significantly higher than that of patients with type II OP ($P = 0.008$). The fever rate of patients with severe OP was significantly higher than that of patients with mild to moderate OP ($P = 0.005$), the fever rates of patients with fresh fracture and operation were significantly higher than those of patients without fresh fracture or operation ($P = 0.000$). The fever rate of patients with previous zoledronic acid use history was significantly lower than patients without zoledronic acid use history ($P = 0.000$). There was no significant difference in fever rate between male and female patients ($P = 0.592$). See Table 2.

Table 2
Influence of various factors on acute febrile reaction induced by zoledronic acid in the treatment of primary osteoporosis

	Factors	Fever group	No fever group	Fever rate	χ^2 value	P-value
Gender	male	12	28	30.00%	0.287	0.592
	female	163	314	34.17%		
Type of osteoporosis	type I	103	159	39.31%	7.082	0.008
	type II	72	183	28.24%		
Degree of osteoporosis	mild-to-moderate	98	147	40.00%	7.868	0.005
	severe	77	195	28.31%		
fresh fracture	yes	102	128	44.35%	20.395	0.000
	No	73	214	25.44%		
Surgery	yes	97	112	46.41%	24.725	0.000
	No	78	230	25.32%		
Zoledronic acid medication history	yes	9	127	6.62%	61.117	0.000
	No	166	215	43.57%		

Logistic multivariate regression analysis of candidate risk factors

Kappa consistency test was performed for the two factors of fracture and surgery, and the Kappa value was 0.6, indicating consistency. The two factors should not be included in the Logistic multivariate regression analysis at the same time. According to the results of the univariate analysis and the Kappa consistency test, among all factors, the fever or not was taken as the dependent variable, and the type, degree, gender, NLR, surgical intervention, and zoledronic acid medication history were taken as the independent variables. Logistic multivariate regression analysis was performed. Results in Table 3 showed that surgical intervention, type of osteoporosis, and previous zoledronic acid administration were the main factors influencing ADR of acute fever. The risk of fever was 1.975 times higher in surgical patients than in non-surgical patients. Patients with type I OP had 2.137 times higher fever risk than patients with type II OP. The fever risk in patients with previous zoledronic acid use was 0.124 times that in patients with first zoledronic acid.

Table 3
Multivariate logistic regression analysis of the influencing factors of acute febrile reaction after medication

Factors		The OR value	95%CI	P-value
Type of osteoporosis	typeⅠ	2.137	1.400~3.263	0.000
	typeⅡ	0.468	0.306~0.715	
Degree of osteoporosis	mild-to-moderate	1.268	0.839~1.917	0.260
	severe	0.789	0.522~1.192	
Gender	male	0.929	0.428~2.016	0.852
	female	1.077	0.496~2.336	
NLR		1.006	0.950~1.065	0.838
Surgery	yes	1.975	1.242~3.139	0.004
	no	0.506	0.319~0.805	
Zoledronic acid medication history	yes	0.124	0.058~0.265	0.000
	no	8.041	3.780~17.108	

ROC curve analysis of three independent risk factors response to acute febrile reaction

The results of ROC curve analysis in Figure 2 showed that the area under the curve of surgical intervention, osteoporosis type, and previous zoledronic acid medication history was 0.654 (95% CI: 0.605-0.703), 0.437 (95% CI: 0.385-0.489) and 0.340 (95% CI: 0.294-0.386), respectively, suggesting that surgical intervention, type I OP and previous zoledronic acid medication history have particular value in predicting the acute febrile reaction of zoledronic acid.

Influence of surgical site on the acute febrile reaction of zoledronic acid

The Chi-square test showed that patients with joint fracture fever rates were significantly higher than those with spinal fracture among surgical patients treated with zoledronic acid ($P = 0.034$). However, in the further comparison of fever rate within the group, there was no significant difference between patients with femoral neck and intertrochanteric fractures or between thoracic and lumbar fractures ($P > 0.05$). See Table 4.

Table 4
Influence of surgical site on the acute febrile reaction of zoledronic acid

	Factors	Fever group	No fever group	Fever rate	χ^2 value	P-value
Surgical site of fracture	joint fracture	30	23	56.60%	4.5	0.034
	spine fracture	37	59	38.54%		
Joint fracture surgery	femoral neck fracture	18	16	52.94%	0.0086	0.93
	intertrochanteric fracture	6	5	54.55%		
Spinal fracture surgery	thoracic vertebra fracture	12	28	30.00%	2.56	0.11
	lumbar vertebra fracture	22	25	46.81%		

Discussion

Zoledronic acid is a compound containing nitrogen bisphosphate. At present, most researchers believe that zoledronic acid, an analog of pyrophosphate, has a strong affinity for bone, especially in the sites where osteoclasts are active and is easy to be absorbed by osteoclasts. Reducing the adherence of osteoclasts on the bone surface, zoledronic acid inhibits activity of osteoclasts, promotes apoptosis, and reduces osteolytic lesions and bone resorption. It has also been suggested that zoledronic acid can induce the apoptosis of osteoclasts and their precursors by inhibiting the mevalonate pathway or interfering with the normal cell cycle, thus playing an anti-bone resorption role. Zoledronic acid inhibits the key enzyme of the mevalonic acid pathway in osteoclasts and prevents the isoprene of small G protein, which makes the function of osteoclasts unable to be maintained normally and promotes their apoptosis. Bisphosphonates can bind to hydroxyapatite in bone, specifically bind to the bone surface where bone transformation is active and inhibit bone resorption by osteoclasts. Zoledronic acid is a representative drug of the third generation of nitrogen-containing bisphosphonates, which has a definite anti-osteoporosis effect and is widely used in clinics. Fever is the most common APR in the treatment of osteoporosis with zoledronic acid by intravenous drip. Zoledronic acid can inhibit farnil pyrophosphate synthetase, thereby preventing the conversion of geranyl pyrophosphate in osteoclasts to farnil pyrophosphate. The increased geranyl pyrophosphate activates $\gamma\Delta T$ cells in the body, causing them to release many inflammatory mediators, such as IL-6, TNF- α , and IFN- γ , resulting in fever and other symptoms[4, 5]. In this study, the incidence of acute febrile reaction in treating primary osteoporosis with zoledronic acid was 33.85%, and the febrile degree was mainly low to medium (85.08%). The time of the first-onset of fever was concentrated within 36h (97.71%), and the duration of febrile reaction was mostly concentrated within 0-60h(92.06%). All of which was well tolerated. Univariate analysis of this study showed that NLR, type of osteoporosis, degree of osteoporosis, presence of fresh fracture, presence of

surgery, and history of zoledronic acid use were associated with the acute febrile reaction, which was statistically significant. There was no significant difference in the mean value of leukocytes, neutrophils, and lymphocytes between the fever and non-fever groups. There was no significant gender difference between the febrile group and the non-febrile group. The results showed that the higher the NLR value before zoledronic acid treatment, the more prone to acute febrile reaction. The fever rate of patients with type I osteoporosis was higher than that of patients with type II osteoporosis. The fever rate of patients with mild and moderate osteoporosis was higher than that of patients with severe osteoporosis. Fever rates are also higher in patients with fresh fractures. Patients with surgical intervention had a higher fever rate. Patients with no history of zoledronic acid use had a higher fever rate. In logistic multivariate regression analysis, since the Kappa consistency test was performed for the two factors of fracture and surgery, and the Kappa value was 0.6, there was consistency. The two factors should not be included in Logistic multivariate regression analysis simultaneously, so the fracture factor was not included temporarily. Logistic multivariate regression analysis showed that the presence of surgery, type of osteoporosis, and the history of zoledronic acid administration were the main influencing factors of acute febrile reaction in treating primary osteoporosis in the Department of orthopaedics. The ROC curve analysis of the presence or absence of surgery, type of osteoporosis, and history of zoledronic acid use showed that the most important factor affecting the adverse reaction of fever was the presence of surgery, type of osteoporosis, and history of zoledronic acid use. Therefore, the appropriate medication period can be selected according to the patient's condition to reduce the incidence of acute febrile reaction. Data analysis in this study also showed that the average value of preoperative NLR was 4.08 ± 4.18 in the surgery group, which was higher than the average NLR of the non-surgery group of 2.25 ± 1.55 , and the difference was significant ($P < 0.001$) through t-test statistical analysis. The mean NLR of the fracture group before medication was 3.72 ± 4.01 , which was higher than that of the non-fracture group (2.76 ± 2.53), and the difference was significant ($P < 0.005$). There was no significant difference in the mean NLR between type I and type II OP patients. The results suggest that fracture and operation may promote acute febrile reaction after zoledronic acid administration by enhancing the body's inflammatory response. In previous studies, the study of Öztürk ZA et al.[6] showed that NLR level in patients with osteoporosis was significantly increased, suggesting that inflammation may play an important role in the occurrence and development of osteoporosis. In this study, the higher the NLR value before zoledronic acid treatment, the more prone to acute febrile reaction. The higher the level of NLR before treatment, the stronger the chronic inflammatory state of patients, and the more likely it is to cause APR by cooperating with the release of a large number of inflammatory mediators caused by ZOL intravenous infusion. It can be used as an index to predict APR before medication. The study of Ko Y et al. showed that the secretion of estrogen in postmenopausal women decreased, the RANKL/RANK/OPG signaling pathway was disorderly, and the inflammatory factors such as interleukin (IL) and TNF, which promoted bone resorption, were constantly increased in the body, leading to the increased expression of RANKL in the microenvironment of bone metabolism, thus accelerating bone loss[7]. Furthermore, studies show that[8, 9], sex steroid hormones may participate in regulating bone metabolism of specific gene expression when estradiol (E2) is lack of, through negative feedback, a mechanism to accelerate the secretion of pituitary follicle-stimulating hormone (FSH). FSH can promote bone marrow cells, and immune cells secrete tumor

necrosis factor alpha (TNF alpha) and interleukin (IL), stimulating bone resorption. Combined with our study, the high fever rate after zoledronic acid treatment in postmenopausal osteoporosis patients may be related to the increase of inflammatory factors after estrogen deficiency in the body. This study showed that the fever rate of patients with previous zoledronic acid medication was significantly reduced, which was consistent with domestic and foreign studies. Rossini M et al.'s study showed that total lymphocytes and their subsets were significantly reduced 2 days after ZOL infusion in patients receiving N-BP for the first time. These changes returned to baseline after 1 year, except for a significant reduction in the proportion and an absolute number of $\gamma\delta$ T cells, suggesting for the first time that both intravenous and oral N-BP therapy are associated with a long-term reduction in circulating $\gamma\delta$ T cells, which may explain the lower incidence of APR in patients exposed to N-BP[10]. A growing body of evidence[11, 12] suggests that congenital and adaptive immune responses are required for fracture healing. Immediately after injury, local infiltration of immune cells and immune mediators are required to remove necrotic tissue and initiate angiogenesis. Various cytokines, including interleukin-1 β , IL-6, IL-17, IL-23, and tumor necrosis factor α (TNF- α), are expressed at different stages and play a role in treatment. This initial infiltration of immune cells subsequently suppresses the immune system, leading to enhanced differentiation of osteoblast mesenchymal stem cells and regulatory T (Treg) cells, both of which inhibit the adaptive T cell response and achieve a hypoinmunogenic state at the healing site[13]. In our study, patients with fresh fractures had a higher fever rate after zoledronic acid treatment, which was considered to be related to the early local infiltration of immune cells and immune mediators and the increase of various inflammatory factors after fracture injury. This suggests that, for patients with complicated fractures, we can judge whether fresh fractures occur, choose the appropriate treatment time, predict the occurrence of APR and do some job of prevention and treatment. Studies have shown that surgical injury can put patients in a state of inflammatory reaction and increase inflammatory factors during the perioperative period. Different operations have different surgical sites and methods. The greater the injury to patients, the more the inflammatory factors increased. Compared with open surgery, the increase of inflammatory factors in the patients undergoing minimally invasive surgery is lower. Cassuto J et al.[14] showed that inflammatory mediators (CRP, IL-6, OPN) in patients undergoing joint replacement increased significantly on the first day after surgery and returned to baseline at 6W. Maruna P et al.[15] showed that the common basis of the systemic inflammatory response to surgical trauma is the activation of cytokine cascades accompanied by the release of soluble cytokine receptors. The major cytokine axis stimulates the release of acute-phase protein (APP) from the liver, regulating metabolic pathways and hormonal responses. The study of Li H et al.[16] showed that the rapid rehabilitation surgical nursing program can effectively relieve the negative emotions and pain of patients with hip fractures and reduce inflammation. Our study showed that the higher fever rate of osteoporosis patients in the surgery group after zoledronic acid treatment might be related to the inflammatory state of the body after surgical injury and the increase of inflammatory factors, which is more likely to produce fever reaction in coordination with the APR reaction caused by zoledronic acid. In our study, the fever rate of patients undergoing joint fracture surgery was 56.60%, and that of patients undergoing spinal fracture surgery was 38.54%, $P < 0.05$. This may reflect that different surgical sites and methods have different effects on the inflammatory response. Total hip replacement and other joint surgeries are level 4 surgeries

with a large degree of openness and greater damage than minimally invasive spinal surgery. In the perioperative period, the body has a higher inflammatory response, more inflammatory mediators are produced, and the synergistic effect with zoledronic acid-induced APR reaction is stronger, which increases the fever rate. This suggests that we should pay attention to the increasing fever rate After zoledronic acid treatment in perioperative patients with a fracture or surgical intervention in the Department of orthopaedics. The timing of zoledronic acid treatment after surgery needs further study, and it can also be combined with rapid rehabilitation surgical nursing program. And for the patients with joint fracture surgery and open surgery, more attention should be paid. The limitation of this study is that the collection of bone metabolism indicators is not enough, the postoperative medication time is not completely unified, the preoperative hydration routine, but the application of NSAIDs drug prevention is not standardized. In conclusion, when zoledronic acid is used to treat patients with primary osteoporosis, an acute febrile reaction may occur. In the Department of orthopaedics, patients with surgical treatment, type I osteoporosis, and no history of zoledronic acid use are more likely to have an acute febrile reaction when zoledronic acid is given intravenously. Choosing a zoledronic acid treatment plan for osteoporosis needs further study, such as preoperative medication or after a certain interval of time, and pay close attention to the patients prone to acute febrile reaction according to the above indicators. The application of zoledronic acid in orthopaedic surgery patients during hospitalization has its limitations. Future use of denosumab may make up for this deficiency.

Abbreviations

ROC

Receiver operating curve

OP

osteoporosis

DXA

dual-energy X-ray absorptiometry

NLR

neutrophil to lymphocyte ratio

APR

acute phase response

Declarations

Ethics approval and consent to participate

The Medical Ethics Committee of Shengjing Hospital Affiliated to China Medical University approved the study (Ethics application number: 2021PS724K). Considering that this work was a retrospective study, the ethics committee waived the requirement for informed consent from patients.

Consent for publication

Not applicable.

Availability of data and materials

The data supporting the conclusion of this article is available on request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HW and SZ are co-first authors. HW, SZ, and YL put forward the study ideas, conducted and wrote the main manuscript text, HW and SZ prepared figures and tables. HW, SZ, YL, YT, EZ, and RX participated in research design and data analysis. During the manuscript preparation, all authors discussed the results. the manuscript were supervised by MSH, HG, and SJ. All authors reviewed the manuscript.

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Figures

Figure 1

Distribution of fever degree, Occurrence time, and Duration of acute febrile response to zoledronic acid treatment in primary osteoporosis

Figure 2