



Original Article

# Clinical analysis of medication related osteonecrosis of the jaws: A growing severe complication in China



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## KEYWORDS

Bisphosphate;  
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Risk factor;  
Treatment

**Abstract** *Background/purpose:* Medication-related osteonecrosis of the jaws (MRONJ) is an unusual but quite serious complication. However, its mechanism remains unclear, and its treatment protocol is still controversial.

*Materials and methods:* Our study involved 201 osteonecrosis of the jaw (ONJ) patients from September 2006 to March 2017. We analyzed risk factors, clinical characteristics, treatment, etc., by comparing MRONJ with other ONJs.

*Results:* Among 201 patients, MRONJ accounted for 14.71% and it presented a consistent increase tendency. In comparison with other ONJs, we considered advanced age, maxilla lesion, diabetes mellitus, tooth extraction, especially multi-teeth extraction as risk factors ( $P < 0.0125$ ). Our study demonstrated that maxillary lesion was associated with an advanced stage and it was inclined to worse prognoses. We also found MRONJ had little correlation to Actinomyces infection. Surgical treatment could improve patients' condition successfully ( $P > 0.05$ ). 81.3% patients with advanced stage showed complete or partial healing lesions after surgery.

*Conclusion:* Advanced age, maxilla lesion, diabetes mellitus, tooth extraction seem to be important triggering factors for MRONJ. Clinicians and surgeons should pay attention to maxillary lesions as it is related to severe symptoms and unfavorable prognosis. Once diagnosed as MRONJ, surgery is an effective treatment for patients with advanced stage.

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## Introduction

Osteonecrosis of the jaw (ONJ) is a common oral and maxillofacial surgery disease. Since 2003, a new sort of ONJ, Bisphosphonate related osteonecrosis of the jaws (BRONJ), has been observed through ever increasing case reports.<sup>1</sup> Briefly, BRONJ is an unusual but quite serious complication of bisphosphonate (BP) therapy in patients suffering from osteoporosis or malignancies, such as multiple myeloma, breast cancer, prostate cancer, etc. In 2014 AAOMS' position paper,<sup>2</sup> BRONJ was replaced by MRONJ (Medication-related osteonecrosis of the jaws), as new drugs, for example, denosumab,<sup>3,4</sup> bevacizumab can also lead to osteonecrosis of the jaws. Though the incidence of MRONJ remains relatively low (0.7–6.7% for IV BPs, 0.1–0.21% for oral BPs),<sup>2</sup> it is lack of effective treatment protocol. Neither surgery nor conservative therapy can thoroughly eliminate patients' symptoms and reach complete healed oral mucosa. In addition, the pathogenesis of MRONJ is unclear even though a great number of researchers have been working on it. Possible hypotheses include inhibition of bone remodeling, anti-angiogenesis effect, bacterial infection, immunity dysfunction and direct cytotoxicity.<sup>5</sup> In China, a growing number of patients with osteoporosis, malignancies or bone cancer metastasis get in touch with BPs. Consequently, the incidence of MRONJ keeps rising. Though it can be easily diagnosed following the guidance of AAOMS,<sup>2,6</sup> difficulty lies in the treatment of MRONJ. The aim of our study is to compare MRONJ with other ONJs in West China Hospital from growing tendency, risk factors, clinical characteristics, treatment and outcomes, and so on, in order to propose guidelines customized for China population.

## Materials and methods

The database of the West China Hospital of Stomatology was searched from September 2006 to March 2017. Patients who visited the West China Hospital of Stomatology and diagnosed with either osteonecrosis of the jaw or osteomyelitis of the jaws were included. The inclusion criteria of MRONJ is according to AAOMS' definition,<sup>2</sup> and the main exclusion criteria of MRONJ were osteonecrosis after radiotherapy in head and neck area and obvious metastatic infiltration of the jaw. Patients who developed into osteonecrosis after bone graft were also excluded. *This study has*

*been approved by the Regional Ethics Committee Investigation of West China Hospital of Stomatology (WCHSIRB-D-2017-060).* 201 patients were eventually selected into the study. Considering the classification of previous study<sup>7</sup> as well as the cause of osteonecrosis, patients were classified as five groups in our study:

1. Medication related osteonecrosis of the jaws (MRONJ) group: patients have a previous or ongoing bisphosphonate treatment history but no head and neck radiation history. Our study didn't find any patients using denosumab or other drugs.
2. Osteoradionecrosis (ORN): Patients went through head and neck radiotherapy before osteonecrosis occurred on the mandible or maxilla.
3. Odontogenic osteonecrosis: Patients with dental infections, such as pericoronitis, developed into osteonecrosis or osteomyelitis with sequestra.
4. Trauma and surgical induced osteonecrosis: Patients were previously exposed to oral or maxillofacial trauma, leading to osteonecrosis or osteomyelitis with sequestra. Or patients went through oral and maxillofacial surgery, subsequently suffered from postoperative infection.
5. Cause-Unknown: Patients with no clear cause.

In the current study, in most cases, we compared the MRONJ group with other groups to figure out specific MRONJ risk factors and other useful statistics.

## Statistical analysis

SPSS (version 21.0, SPSS Inc., Chicago, IL, USA) was used to analyze the collected data. We analyzed descriptive statistics, and results were expressed in mean, standard deviation, frequency, percentage for different variables.

The Anova was applied for the study of the association of qualitative variables. To detect any differences between qualitative variables, the Pearson Chi Square test or Fisher's exact test, Bonferroni correction, Mann–Whitney U test were used as appropriate.  $P \leq 0.05$  were considered statistically significant.

## Results

201 patients were selected into our study. According to the statistics, odontogenic osteonecrosis was the most frequent

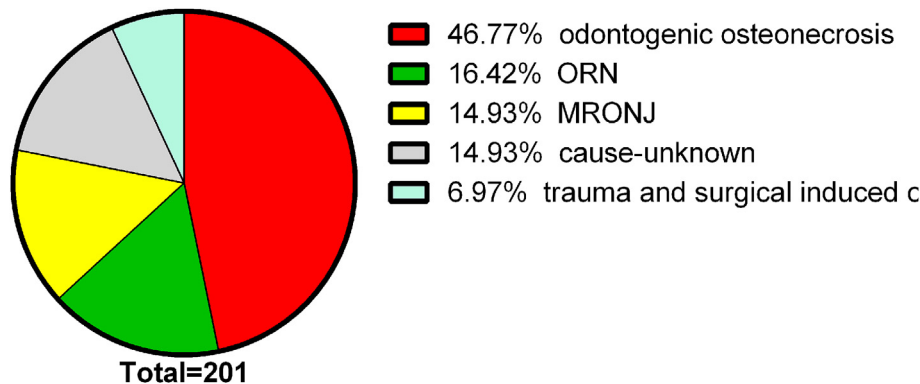


Figure 1 The fraction of each osteonecrosis.

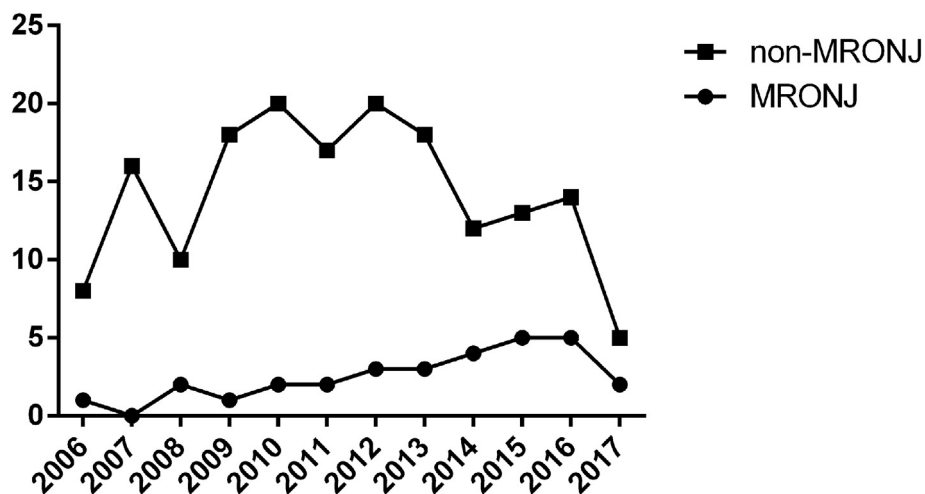


Figure 2 Number of MRONJ and non-MRONJ from 2006 to 2017.

Table 1 BP<sup>a</sup> type and systemic disease of MRONJ<sup>b</sup> patients.

Original disease	No. of MRONJ <sup>b</sup> patients (%)
prostate cancer	7 (23.3%)
osteoporosis	7 (23.3%)
breast cancer	5 (16.7)
multiple myeloma	3 (10%)
lung cancer	1 (3.3%)
cervical cancer	1 (3.3%)
leukemia	1 (3.3%)
BP <sup>a</sup> type	No. of MRONJ <sup>b</sup> patients (%)
Zoledronate	12 (50%)
Pamidronate	1 (4.2%)
Alendronate	4 (16.7%)

<sup>a</sup> BP: bisphosphonate.

<sup>b</sup> MRONJ: medication related osteonecrosis of the jaws.

osteonecrosis, accounting for 46.77%. The second biggest groups were osteoradionecrosis. MRONJ as well as cause-unknown osteonecrosis followed (Fig. 1), and MRONJ presented a consistent increase tendency (Fig. 2). The bisphosphonate most commonly used was zoledronate ( $n = 12$ , 50%). The most related systemic diseases were

prostate cancer and osteoporosis (23.3%). Other systemic diseases included breast cancer, multiple myeloma et al (Table 1).

#### Age, gender and location

The median age of MRONJ patients was 64.43 years (range, 32–87 years), older than all other groups. There were statistically differences between MRONJ group and odontogenic, cause unknown, trauma & surgical group (ANOVA,  $P < 0.001$ ). With regard to gender, the sex ratio (male: female) of MRONJ group was 1.14, and it did not show any statistical significant differences. As for the location of the osteonecrosis, 11 patients had MRONJ lesions located in the maxilla, in contrast to 19 in the mandible, and none occurred in both the jaws. The fraction of maxillary lesions in the MRONJ group was higher than all other groups (Bonferroni correction,  $P < 0.0125$ ) (Table 2).

#### Risk factors

Among those patient with MRONJ, five patients had hypertension (16.7%), six patients had diabetes mellitus (20%). Corticosteroid and immunosuppressant usage accounted for 13.3%. MRONJ group had more diabetes

Table 2 Demographic analysis of the collected data.

Group	Patient number	Age (mean $\pm$ SD)	Gender ratio male: female	Location ratio maxilla: mandible
MRONJ <sup>a</sup>	30 (14.93%)	64.43 $\pm$ 14.041	16:14 (1.14)	11:19 (0.58)
ORN <sup>b</sup>	33 (16.42%)	55.61 $\pm$ 11.630	24:9 (2.67)	4:30 (0.13) <sup>d</sup>
Odontogenic osteonecrosis	94 (46.77%)	46.64 $\pm$ 17.218	54:40 (1.35)	10:85 (0.12) <sup>d</sup>
Trauma & surgical induced osteonecrosis	14 (6.97%)	33.00 $\pm$ 22.405	9:5 (1.8)	0:14 <sup>c</sup>
Cause-Unknown	30 (14.93%)	45.33 $\pm$ 23.072	12:18 (0.67)	5:27 (0.19) <sup>d</sup>

<sup>a</sup> MRONJ: medication related osteonecrosis of the jaws.

<sup>b</sup> ORN: Osteoradionecrosis.

<sup>c</sup> In surgery and trauma groups, none of patients' lesion occurred in the maxilla.

<sup>d</sup> ORN, Odontogenic osteonecrosis, Cause-Unknown groups had 1, 1, 2 lesions occurred in both the jaws respectively.

**Table 3** General and local risk factor of ONJs.<sup>a</sup>

Risk factor	No. of MRONJ <sup>b</sup> patients (%)	No. of ORN <sup>c</sup> patients (%)	No. of OO <sup>d</sup> patients (%)	No. of TSO <sup>e</sup> patients (%)	No. of CU <sup>f</sup> patients (%)
<b>General risk factor</b>					
hypertension	5 (16.7%)	4 (12.1)	9 (9.6%)	0	5 (16.7%)
diabetes mellitus	6 (20%)*	2 (6.1%)	3 (3.2%)*	0	0
Corticosteroid and immunosuppressant	4 (13.3%)	1 (3.0%)	6 (6.4%)	0	3 (10%)
<b>habit</b>					
smoke	11 (36.7%)	12 (36.4%)	36 (38.3%)	5 (35.7%)	8 (26.7%)
alcohol	9 (30%)	12 (36.4%)	34 (36.2%)	4 (18.6%)	8 (26.7%)
<b>local risk factor</b>					
Tooth extraction	24 (80%)*	9 (27.3%)*	65 (69.1%)	2 (14.3%)*	0*
Multi-extraction <sup>g</sup>	14 (58.3%)*	2 (22.1%)	13 (20%)*	2 (100%)	0
Secondary extraction <sup>h</sup>	3 (12.5%)	0	6 (9.2%)	0	0
Periodontal disease	5 (16.7%)	5 (15.2%)	3 (3.2%)	1 (7.1%)	2 (6.7%)
Poor oral hygiene	8 (26.7%)	8 (24.2%)	12 (12.8%)	4 (18.6%)	7 (23.3%)
Inappropriate prosthesis	3 (10%)	1 (3.0%)	9 (9.6%)	2 (14.3%)	2 (6.7%)

Data with asterisks means there are statistically difference between MRONJ and these groups.

<sup>a</sup> ONJ: osteonecrosis of the jaw.

<sup>b</sup> MRONJ: medication related osteonecrosis of the jaws.

<sup>c</sup> ORN: Osteoradionecrosis.

<sup>d</sup> OO: Odontogenic osteonecrosis.

<sup>e</sup> TSO: Trauma and surgical induced osteonecrosis.

<sup>f</sup> CU: Cause-Unknown.

<sup>g</sup> Multi-extraction: more than one tooth extracted one time.

<sup>h</sup> Secondary extraction: teeth extracted for more than one time.

**Table 4** Staging of medication-related osteonecrosis of the jaw.

Staging	Symptoms and signs
Stage 0	patients without specific exposed necrotic bone, but with non-specific symptoms or clinical and imaging findings, such as pain, radiographic non-healing bone in extraction sockets.
Stage 1	Patients with exposed and necrotic bone or fistulas but no evidence of infection.
Stage 2	Patients with exposed and necrotic bone or fistulas as well as clinical infection symptoms.
Stage 3	Based on stage II, patients with severe clinical presentations, such as pathologic fracture, extra-oral fistula, osteolysis extending to the maxillary sinus floor or inferior border of the mandible.

mellitus cases than all other groups and it showed statistically differences between MRONJ group and odontogenic cases (Bonferroni correction  $< 0.0125$ ). Speaking of drinking and smoking, 36.7%MRONJ patients were smokers. 30% MRONJ patients had drinking habits, but we didn't find any statistically differences between MRONJ and other groups (Table 3).

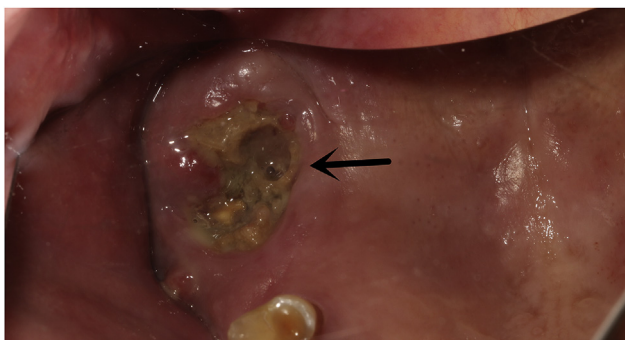
Our study also analyzed local triggering factors in MRONJ group involving tooth extraction ( $n = 24, 80\%$ ), periodontal disease ( $n = 5, 16.7\%$ ), poor oral hygiene ( $n = 8, 26.7\%$ ), inappropriate prosthesis ( $n = 3, 10\%$ ). 28 patients had local

risk factors on record, while only two patients developed MRONJ spontaneously. Nevertheless, only tooth extraction presented statistically differences with other groups. MRONJ had more patients whose teeth were extracted, pretty higher than ORN group, cause unknown group, trauma and surgical group ( $P < 0.001$ ) (Table 3).

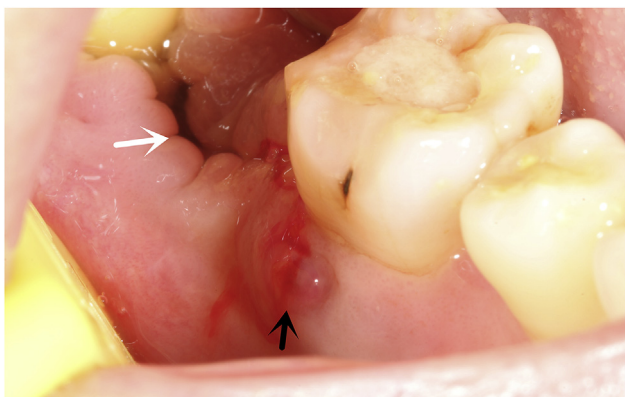
### Clinical presentations and imaging features

Of 30 MRONJ patients, nine patients presented stage III lesions, 17 patients presented stage II lesions, only one patient showed stage I lesions. Besides, three patients presented stage 0 lesions. There were statistically differences between MRONJ stage and location (Mann–Whitney U test,  $P < 0.05$ ). Maxilla lesions inclined to an advanced stage based on our data (Staging of Medication-Related Osteonecrosis of the Jaw in Table 4).

According to our statistics, MRONJ's common symptoms included exposed bone (Fig. 3), pain or discomfort, swelling, pus (Fig. 4), fistula (Fig. 5). Other symptoms were recorded in Table 5. Except for exposed bone, no statistically differences between MRONJ and other groups were found. MRONJ presented the highest rate when it came to the exposed bone ( $P < 0.001$ ). All MRONJ patients were examined with dental panoramic radiograph or Cone beam CT. Common imaging features included sequestra (Fig. 6), osteolysis, osteosclerosis (Fig. 7). Other imaging features were recorded in Table 6. Osteolysis, irregularity of the cortical margins, maxillary sinusitis showed statistically differences (Bonferroni correction,  $P < 0.0125$ ). MRONJ group had more cases with maxillary sinusitis than other



**Figure 3** Clinical image of mandibular uncovered, necrotic bone in a MRONJ patient.



**Figure 4** Clinical image of pus and skin fistula and pus in an MRONJ patient.



**Figure 5** A female patient who had BPs usage history for breast cancer, six months after tooth extraction: Clinical image of the oral fistula (black arrow) and uncovered extraction socket (white arrow).

**Table 5** Clinical presentations of MRONJ<sup>a</sup> patients.

Clinical presentations of MRONJ <sup>a</sup> patients	No. of MRONJ <sup>a</sup> patients (%)
Exposed bone	27 (90%)
Pain or discomfort	24 (80%)
Swelling	18 (60%)
Pus	17 (56.7%)
Trismus	8 (26.7%)
Paresthesia	5 (16.7%)
Oral fistula	7 (23.3%)
Skin fistula	4 (13.3%)
Halitosis	2 (6.7%)
Hemorrhage	2 (6.7%)

<sup>a</sup> MRONJ: medication related osteonecrosis of the jaws.

groups, while MRONJ had fewer cases when it came to another two imaging features.

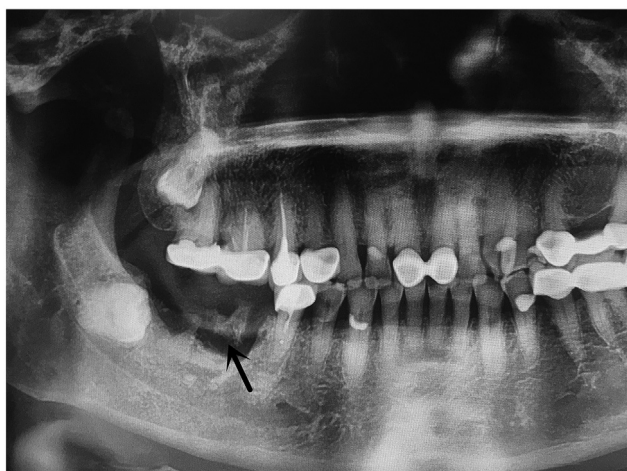
### Histopathologic and microbiological findings

20 patients in MRONJ group underwent biopsy. Inflammatory infiltrates, Sequestra were detected in most patients. Necrotic foci, colonization with pathogens, fibrous hyperplasia, bone hyperplasia was also detected among these patients. However, there were no statistically differences between MRONJ and all other groups. A total of 39 patients (8 in MRONJ group) underwent microbiological examination. Bacterium was isolated from pus from exposed bone or fistula. In MRONJ group,  $\alpha$ -hemolytic streptococci, neisseria, prevotella intermedia, coagulase negative staphylococci, Corynebacterium were found. Notably, we did not find any patients infected with Actinomyces. There were also no statistically differences between MRONJ and all other groups ( $P > 0.05$ ).

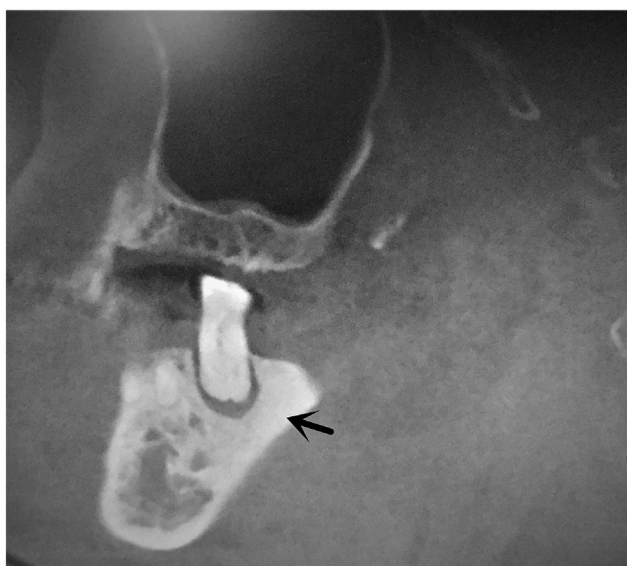
### Treatment and outcome

16 MRONJ patients, consisting of all nine stage III patients, underwent surgical treatment (sequestrectomy, deep curettage, segmental resection of the jaw boneset al.). Other 11 patients underwent conservative treatment (antibiotic therapy, debridement et al.). Three patients gave up treatment because of poor general condition or financial problems. In ORN group, 48.5% went through surgical treatment. While among other three groups, over 90% patients underwent surgical treatment.

After surgical treatment, 81.3% MRONJ patients showed complete or partial healing lesions, while other three patients' condition deteriorated. Conversely, only five patients (45.5%) who underwent conservative treatment showed complete or partial healing lesions. Six patients didn't show any improvement. Evolution of surgical treatment was better than conservative treatment in the present study though this difference did not reach statistically significant levels ( $P > 0.05$ ) (Table 7). It is worth noting that maxillary lesions were more inclined to worse prognoses ( $P < 0.05$ ), six maxillary lesions ended up as no improvement or extended lesions, while only four maxillary lesions



**Figure 6** Dental panoramic radiography showing a sequestra in the right mandible region (black arrow).



**Figure 7** Cone beam CT showing osteosclerosis around the loose tooth (black arrow).

**Table 6** Imaging features of MRONJ<sup>a</sup> patients.

Imaging features of MRONJ <sup>a</sup> patients	No. of MRONJ <sup>a</sup> patients (%)
Sequestra	16 (53.3%)
Osteolysis	17 (56.7%)
Osteosclerosis	12 (40%)
Non-healing extraction socket	8 (26.7%)
Periosteal reaction	7 (23.3%)
Irregularity of the cortical margins	4 (13.3%)
Maxillary sinusitis	8 (26.7%)
Involvement of mandibular canal	2 (6.7%)
Pathologic fracture	1 (3.3%)

<sup>a</sup> MRONJ: medication related osteonecrosis of the jaws.

**Table 7** Treatment outcomes of MRONJ<sup>a</sup> patients.

Treatment	No. of MRONJ <sup>a</sup> patients	No. of improvement	No. of no improvement
Surgical treatment	16	13 (81.3%)	3 (18.7%)
Conservative treatment	11	5 (45.5%)	6 (54.5%)

<sup>a</sup> MRONJ: medication related osteonecrosis of the jaws.

ended up as complete or partial healing lesions. In contrast, 63% mandible lesions improved after therapy.

## Discussion

On the basis of the AAOMS' position paper,<sup>2</sup> MRONJ patients should suit 3 characteristics: 1) current or previous treatment with antiresorptive or antiangiogenic agents, 2) exposed, necrotic bone or fistula in the maxillofacial region which has maintained for at least 8 weeks and 3) no history of radiotherapy to the jaws. However, our study only involved patients with bisphosphonate usage, without any new drugs such as denosumab and ONJ was divided into five groups. A previous study shared a similar classification and BRONJ accounted for 45%.<sup>7</sup> Though MRONJ cases in our study only accounted for 14.71%, it showed a dramatically consistent increase tendency as previously described.<sup>7,8</sup> MRONJ made up 6.74% from 2006 to 2010, whereas it climbed up to 20.87% in last five years. This is probably because BPs were just started to be widely used in China in recent years. MRONJ is still a rare drug-related side effect in China but predictably, it tends to be rapidly increased in 10 years owing to numerous BPs prescription.

It is important to emphasize that 36.67% MRONJ lesions occurred in the maxilla, quite higher than other groups. This ratio is pretty higher than most of the previous articles.<sup>8-10</sup> Oral and maxillofacial surgeons are supposed to pay attention to maxillary MRONJ lesions, since maxilla lesions can lead to severe symptoms, such as maxillary sinusitis, perforation of maxillary sinus. According to the result of Nisi et al.,<sup>11</sup> maxillary lesion was associated with a worse MRONJ stage, and the present study reach the same conclusion too. And our study also found out maxillary lesion were more inclined to worse prognoses. According to our data, median age of MRONJ group was 64.43, older than all other groups ( $P < 0.001$ ), which coincides with the data collected previously.<sup>7</sup> A possible explanation might be that older people are more likely to suffer from osteoporosis or malignancies, and BPs are always prescribed to them. With regard to gender, our data showed men and women had nearly equal chance to get involved in MRONJ, which is at odds with previous articles. Several authors observed more women are affected by MRONJ.<sup>8,12,13</sup> This might because prostate cancer is the one of the most frequent reason for BPs therapy in the present study, whereas prostate cancer only refers to male patients.

When it comes to local risk factors, 93.3% patients went through dental procedures or had dental problems. Only

two patients developed MRONJ spontaneously. This ratio is close to published results.<sup>7,13</sup> As the most frequent invasive dental procedure, tooth extraction existed in 80% MRONJ patients and statistically differences were found ( $P < 0.001$ ). Our study also analyzed the effect of multi-extraction, in parallel with exposure bony size reported previously.<sup>14</sup> Considering direct cytotoxicity as a hypothesis, we speculated that maybe exposure size was association with the occurrence of MRONJ. Our results confirmed this consumption ( $P < 0.015$ ). A previous study carried out an animal experiment, concluded that SD rats all developed MRONJ after repeated surgical extraction (second molar was extracted one week after first molar was extracted).<sup>15</sup> Based on this animal experiment, we also analyzed the effect of repeated extraction. However, it turned out that repeated extraction did not bring about higher prevalence of MRONJ. Other risk factors, such as periodontal disease, inappropriate prosthesis, poor oral hygiene, had been discussed as risk factors by many published studies.<sup>16–18</sup> Nevertheless, these differences did not reach statistically significant levels in the current study. In regards to the systemic condition, diabetes mellitus was the risk factor for MRONJ based on current data. However, our study did not find any statistically significant differences regarding hypertension, corticosteroid, smoking and alcohol. While several publications showed opposite results.<sup>9,11,19</sup>

With the current available data, exposed bone was the only sign that showed statistically significant differences between MRONJ and all other groups ( $P < 0.001$ ). This is consistent with the definition of MRONJ, which treats exposed bone as a necessary condition. With regard to imaging features, most findings could be found in both MRONJ and other groups. Of 11 MRONJ patients with maxilla lesions, 8 had evidence of maxillary sinusitis, parallel with the published literature.<sup>20</sup> MRONJ group significantly had more maxillary sinusitis cases in contrast to other groups. We speculated this was because MRONJ group had more lesions in the maxilla (36.7%). Furthermore, maxillary lesions were more likely to cause MRONJ of advanced stage ( $P < 0.05$ ).

In the current study, histopathologic and microbiological findings did not show any statistically differences between MRONJ and other groups. According to the previous literature, Actinomyces played an important role in the course of MRONJ,<sup>21</sup> it estimated 73.2% (407 of 556) of the patients reported previously infected with Actinomyces. Anavi et al.<sup>19</sup> even isolated Actinomyces colonies in all 52 patients. Analogously, 66.7% patients were detected with Actinomyces colonization in a study from Spain.<sup>14</sup> However, our data did not find any patients infected with Actinomyces by microbiological examination. Three MRONJ patients' histopathologic examinations showed colonization with pathogens, but unfortunately, we couldn't find out whether it is Actinomyces or not. According to our results, MRONJ has little correlation to Actinomyces infection.

53.3% MRONJ patients underwent surgical procedure consisting of all stage III and seven stage II patients who had obvious sign of mobile bony sequestra. Conservative surgery was performed to other patients. Even though there were no statistically differences, surgical treatment's evolution was better than conservative treatment. 81.3% patients showed complete or partial healing lesions after surgery compared with 45.5% patients who accepted conservative

treatment. Other authors also reported successful outcomes after surgery. Pichardo et al.<sup>10</sup> found all 74 MRONJ patients cured through surgical protocol. Holzinger et al.<sup>22</sup> drew the conclusion that effective surgery was able to improve the stage of MRONJ. Janovska et al.<sup>23</sup> found surgical treatment could lead to complete healing but it bore the risk of progression of the osteonecrosis and should be carefully planned under the control of patient's general health status.

Medication related osteonecrosis of the jaws is growing rapidly in China due to the wide use of Bisphosphonates. However, it is impossible to terminate prescription of BPs because most MRONJ patients receive BPs therapy to fight against malignancies or osteoporosis. Therefore, prevention strategies are essential for these patients.<sup>24,25</sup> In conclusion, our retrospective study found some MRONJ risk factors like advanced age, maxilla lesion, diabetes mellitus, chemotherapy, multi-teeth extraction. In addition, MRONJ has scarce specific clinical, imaging, histopathologic and microbiological features. We also claimed that surgical treatment could improve condition successfully in advanced stage patients. However, because of limited cases, and some patients' information were incomplete, the result could be specific to our study. To figure out the pathogenesis of MRONJ and suited treatment protocol thoroughly, further studies with large series should keep focusing on MRONJ.

## Conflicts of interest

The authors have no conflicts of interest relevant to this article.

## Acknowledgement

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