



REVIEW ARTICLE

# Clinical characteristics and treatment of clavicular osteomyelitis: a systematic review with pooled analysis of 294 reported cases

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**Background:** It is usually difficult to diagnose clavicular osteomyelitis (OM), and treatment is delayed because of its rarity. This study aimed to summarize clinical characteristics and treatment of this disease.

**Methods:** We searched the PubMed and Embase databases to identify English studies that reported on clavicular OM from January 1980 through December 2016. Effective data were pooled for analysis.

**Results:** In total, 111 studies comprising 294 cases (bacterial OM, 146; nonbacterial OM, 148) were included, with a sex ratio of 1.89:1 indicating female predilection. Overall, the median age at diagnosis was 16 years. The acute to chronic phase ratio was 0.30, with a median symptom duration of 4 months. The most frequently reported symptom was pain (192 cases), followed by swelling (151 cases) and fever (52 cases). Altogether, 86.94% cases of single-site involvement were reported, with the medial side being the most common site (69.95%). The erythrocyte sedimentation rate achieved the highest positive rate (74.44%) before treatment. The total positive rate of culture for bacterial OM was 81.82%, with *Staphylococcus aureus* being the most frequently detected pathogen (44.70%). The average cure rate was 83.52%, with no significant difference between surgical (89.70%) and nonsurgical (79.63%) cases ( $P = .079$ ).

**Conclusions:** Clavicular OM, predominant in female patients and young people, usually occurred at a chronic stage. Pain was the most frequent symptom, with the medial side being the most involved site. The erythrocyte sedimentation rate may be a helpful indicator for diagnosis. Regardless of surgery or nonsurgery, most patients achieved a favorable prognosis.

**Level of evidence:** Level IV; Systematic Review

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**Keywords:** Clavicle; bacterial osteomyelitis; nonbacterial osteitis; chronic recurrent multifocal osteomyelitis; CRMO; SAPHO syndrome; systematic review

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The clavicle, a sigmoid-shaped bone, serves as a connection between the axial and appendicular skeleton in conjunction with the scapula, and it forms the pectoral girdle.<sup>55</sup> Because of its unique shape, position, and function, clavicular fracture is common.<sup>16</sup> In contrast to studies

of clavicular fracture, the number of studies reporting on clavicular osteomyelitis (OM) has remained limited owing to its lower prevalence.

According to different causes, clavicular OM can be classified as bacterial or nonbacterial. Bacterial OM, also known as bone infection, is characterized by inflammation-associated osteolysis, necrosis,<sup>77</sup> and, in the chronic phase, new bone formation simultaneously. Bacterial OM can occur through contiguous, hematogenous, and perioperative routes,<sup>12,75,91,128</sup> with the tibia and femur being the most frequently affected sites.<sup>58,74,89,119</sup> However, such bone infection has seldom been identified in the clavicle.<sup>50</sup>

Nonbacterial OM, first described in 1972 by Giedion et al<sup>46</sup> as a symmetric, chronic, multifocal OM with bone lesions, is an autoinflammatory bone disorder not linked to infectious disease.<sup>50</sup> Different from bacterial OM, nonbacterial OM, also previously known as chronic recurrent multifocal osteomyelitis (CRMO), is characterized by recurring episodes or the persistent presence of one or more sterile OM lesions.<sup>108,109</sup> Currently, nonbacterial OM has become a broad concept with multiple names and types in addition to CRMO, such as synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome, condensing osteitis, and hyperostosis.<sup>57</sup> Despite its wide-ranging definition, the prevalence of nonbacterial OM remains extremely low. For example, the reported prevalence of CRMO ranged from 1:160,000 to 1:2,000,000, with an annual incidence of 1:250,000 to 1:1,000,000.<sup>109</sup> The lesions can affect any bone, with more lesions frequently reported in the metaphyses of the long bones, such as the distal femur, proximal and distal parts of the tibia, and fibula.<sup>125</sup> However, the clavicle is not a frequently involved site.

Because of the low prevalences of both bacterial and nonbacterial OM of the clavicle, most clinicians do not have much experience with this disorder. In addition, highly variable clinical manifestations as well as the lack of consensus for diagnosis often make the diagnosis of clavicular OM more difficult, especially in the case of nonbacterial OM.<sup>108,109</sup> Therefore, to help clinicians better recognize and understand clavicular OM, we performed this study with the aim of summarizing the clinical characteristics and treatment of clavicular OM based on pooled outcomes of reported cases in the literature.

## Methods

### Literature search

A systematic literature search of the PubMed and Embase databases was performed by 2 independent authors to identify studies that reported on the clinical features and management of bacterial and nonbacterial OM of the clavicle between January 1, 1980, and December 31, 2016, with the publication language limited to English. Keywords used in the search were as follows: “clavicle,” “clavicular,” “osteomyelitis,” “osteitis,” and “hyperostosis.”

### Inclusion and exclusion criteria

Only studies that reported on the clinical characteristics and treatment of clavicular OM were considered for inclusion. Case reports, case series, and letters to the editor were also screened. Eligible studies were investigations that focused on either bacterial or nonbacterial OM of the clavicle with available data for pooled analysis. In addition to CRMO, patients with SAPHO syndrome, condensing osteitis, and hyperostosis of the clavicle were also recruited as nonbacterial OM. Exclusion criteria were studies of cases without clavicular OM or osteitis, studies of cases without bacterial OM, and studies without effective data for outcome analysis. In addition, other study types (eg, reviews and clinical surveys) and research fields (eg, radiology and flap surgery) regarding the clavicle were excluded.

### Study identification and data extraction

Two authors independently screened the titles, abstracts, and full texts to ensure that the recruited studies strictly complied with the inclusion criteria. Three reviewers independently participated in the extraction of effective data from all eligible reports. Disagreement about eligibility and harvested data was resolved by discussion, and if necessary, a third reviewer's opinion was consulted to make the final decision.

### Outcome measures

Outcome measures were clinical characteristics, treatment strategies, and clinical efficacy, including the type of OM; patient's sex; age at diagnosis; acute or chronic phase at diagnosis; symptom duration; clinical symptoms; side and site distributions; serum levels of inflammatory biomarkers (white blood cell [WBC] count, erythrocyte sedimentation rate [ESR], and C-reactive protein [CRP] level) before treatment; pathogen culture results for bacterial OM; treatment strategies; and final clinical efficacy.

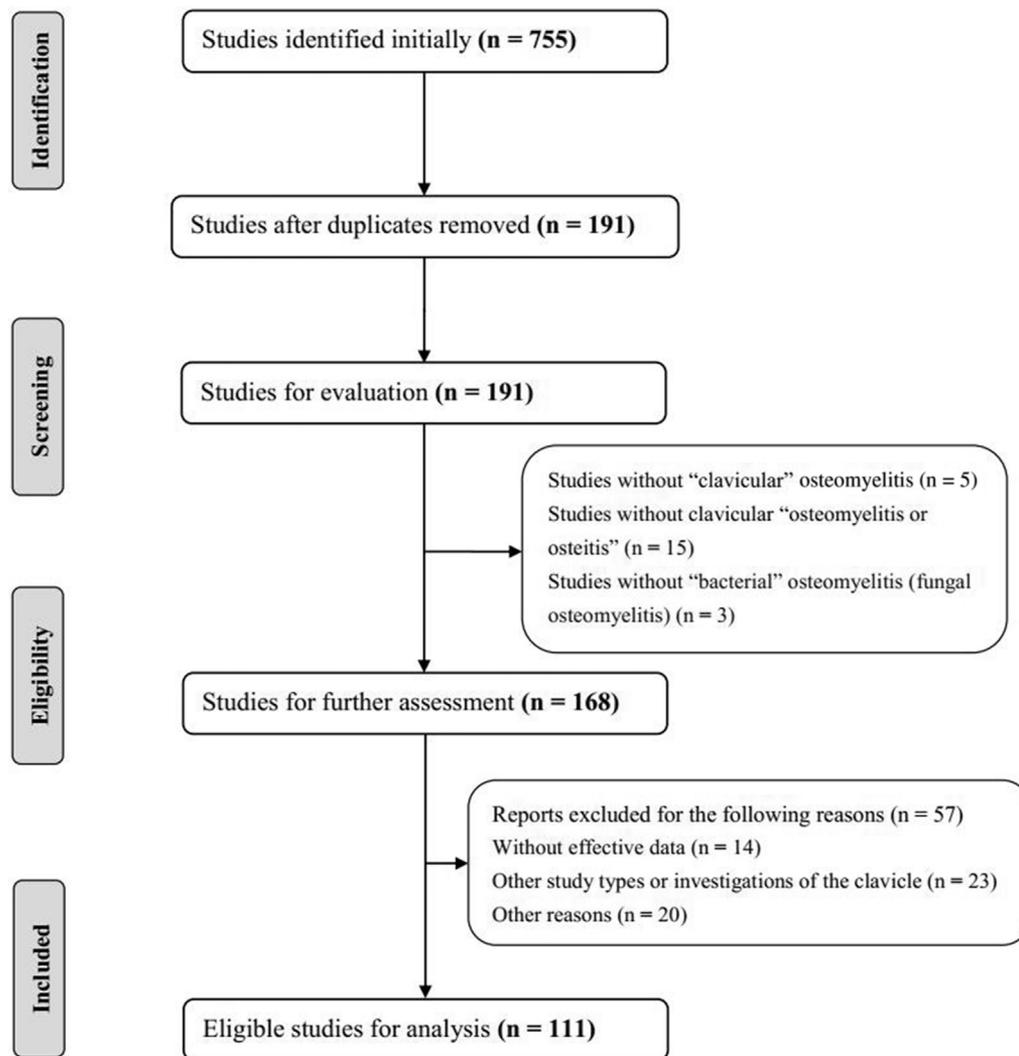
### Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences 17.0 software (SPSS Inc., Chicago, IL, USA). Data distributions were evaluated for normality by using the Kolmogorov-Smirnov test. Continuous variables are expressed as mean  $\pm$  standard deviation or median with interquartile range (IQR), depending on the data distribution. For normally distributed data, the Student *t*-test was used to compare the differences between the 2 independent groups. Otherwise, the Mann-Whitney *U* test was used. Dichotomous variables are expressed as percentages and events with totals. The  $\chi^2$  test was used to compare differences of rates between the 2 different groups. A statistically significant difference was defined as a *P* value  $\leq .05$ .

## Results

### Study identification

A total of 191 potentially relevant English reports were identified initially. After referencing the titles, abstracts,



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram.

and full texts, 111 studies<sup>1-15,17-22,24-40,42-45,47-49,51-54,56,59-73,75,76,79-88,90-95,97-107,110-118,120-124,126-128</sup> with 294 cases were included in the final analysis. The eligibility selection process is shown in [Figure 1](#). The distribution of the total number of eligible patients by geographic location (country) is depicted in [Figure 2](#); the United States was the top country (63 cases), followed by the United Kingdom (45 cases) and India (27 cases).

### Types of clavicular OM

Of 294 cases, 146 patients had bacterial OM, and of those, 31 had *Mycobacterium tuberculosis*-associated OM. Among the 148 patients with nonbacterial OM, 58 cases were reported as CRMO, 16 as SAPHO syndrome, 66 as condensing osteitis, and 8 as sternocostoclavicular hyperostosis.

### Demographics

Of all the included studies with available data of patients' sex, there were 176 female patients and 93 male patients, with a sex ratio of 1.89:1, indicating female predilection. Overall, the median age at diagnosis was 16 years (IQR, 11-42 years). As shown in [Figure 3](#), patients younger than 40 years at diagnosis of clavicular OM accounted for 72.86% (196/269). No significant difference was found in the median age at diagnosis between male patients (median, 22 years; IQR, 11.6-48 years) and female patients (median, 15 years; IQR, 10-37 years) ( $P = .065$ ).

### Disease phase ratio and clinical symptoms

The total numbers of patients in the acute and chronic phases at diagnosis were 54 cases and 182 cases, respectively, with an acute-to-chronic-phase ratio of 0.30. The



**Figure 2** Distribution of the total number of included patients from studies of different countries.

median duration from onset of symptoms to clinical diagnosis was 4 months (IQR, 1-12 months).

Altogether, 524 clinical symptoms from 238 cases were reported, with an average of 2.20 symptoms (range, 1-6 symptoms) for each patient. The most frequently reported symptom was pain (192 cases [36.64%]), followed by swelling (151 cases [28.82%]), fever (52 cases [9.92%]), tenderness (36 cases [6.87%]), sinus (30 cases [5.73%]), erythema (29 cases [5.53%]), discomfort and limitation of motion (20 cases [3.82%]), and local mass (14 cases [2.67%]).

### Distributions of the involved body side and clavicle site

Ninety-two cases had clavicular OM on the left side of the body, and 129 cases and 10 cases had it on the right side and both sides of the body, respectively. With respect to site distribution, 193 patients had a single site affected, and 29 patients had multiple sites affected. The most frequently involved single site was the medial side of the clavicle (135 cases [69.95%]), followed by the sternoclavicular joint (27 cases [13.99%]), midshaft (19 cases [9.84%]), lateral side (11 cases [5.70%]), and acromioclavicular joint (1 case [0.52%]). Among the 29 patients with multiple affected sites, the top sites were the medial side and sternoclavicular joint (23 cases [79.31%]), followed by the midshaft plus lateral side (3 cases [10.34%]) and whole clavicle (3 cases [10.34%]).

### Positive rates and levels of serum inflammatory biomarkers before treatment

Positive rates of the WBC count, ESR, and CRP level before treatment were 19.81% (21/106), 74.44% (99/133), and

40.74% (22/54), respectively. The mean values before therapy were as follows: WBC count,  $10.4 \pm 4.2 \times 10^9/L$  (range,  $3.5\text{--}21 \times 10^9/L$ ); ESR,  $55.9 \pm 32.1$  mm/h (range, 6-167 mm/h); and CRP level,  $36.2 \pm 42.3$  mg/L (range, 1.7-151.0 mg/L).

### Pathogen culture results for bacterial OM

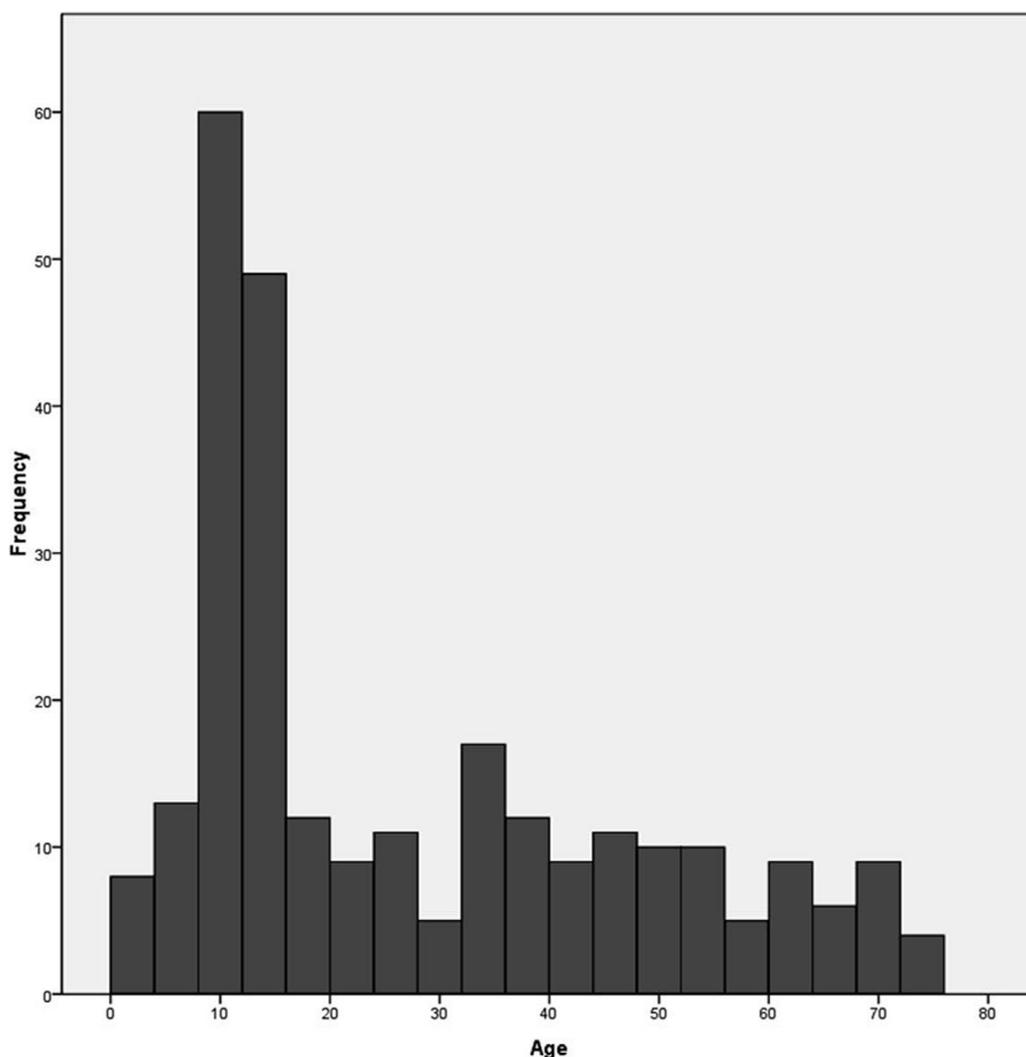
The total positive rate of the cultures was 81.82% (99/121), with 85 patients having a monomicrobial infection and 14 having a multimicrobial infection. Among the 85 cases with a single-pathogen infection, the most frequently detected bacterium was *Staphylococcus aureus* (44.70% [38/85]), followed by *M. tuberculosis* (21.18% [18/85]) and *Pseudomonas aeruginosa* (7.06% [6/85]).

### Treatment strategies and clinical efficacy

Among the 219 patients with a detailed treatment strategy, 81 patients received surgical interventions, and 138 patients selected conservative therapy. Total cure rates for surgically and nonsurgically treated patients were 89.70% (61/68) and 79.63% (86/108), respectively, with no statistically significant difference between the groups ( $P = .079$ ). The most frequently reported surgical strategy was focus curettage (47 cases [58.02%]), followed by partial clavicle resection (16 cases [19.75%]) and total clavicectomy (11 cases [13.58%]), with cure rates of 89.74% (35/39), 93.75% (15/16), and 100% (8/8), respectively.

### Proportions of surgical and nonsurgical cases by time

**Figure 4**, A reveals the total numbers of patients who received surgery and nonsurgery by pooled outcomes from



**Figure 3** Age distribution of patients with clavicular osteomyelitis.

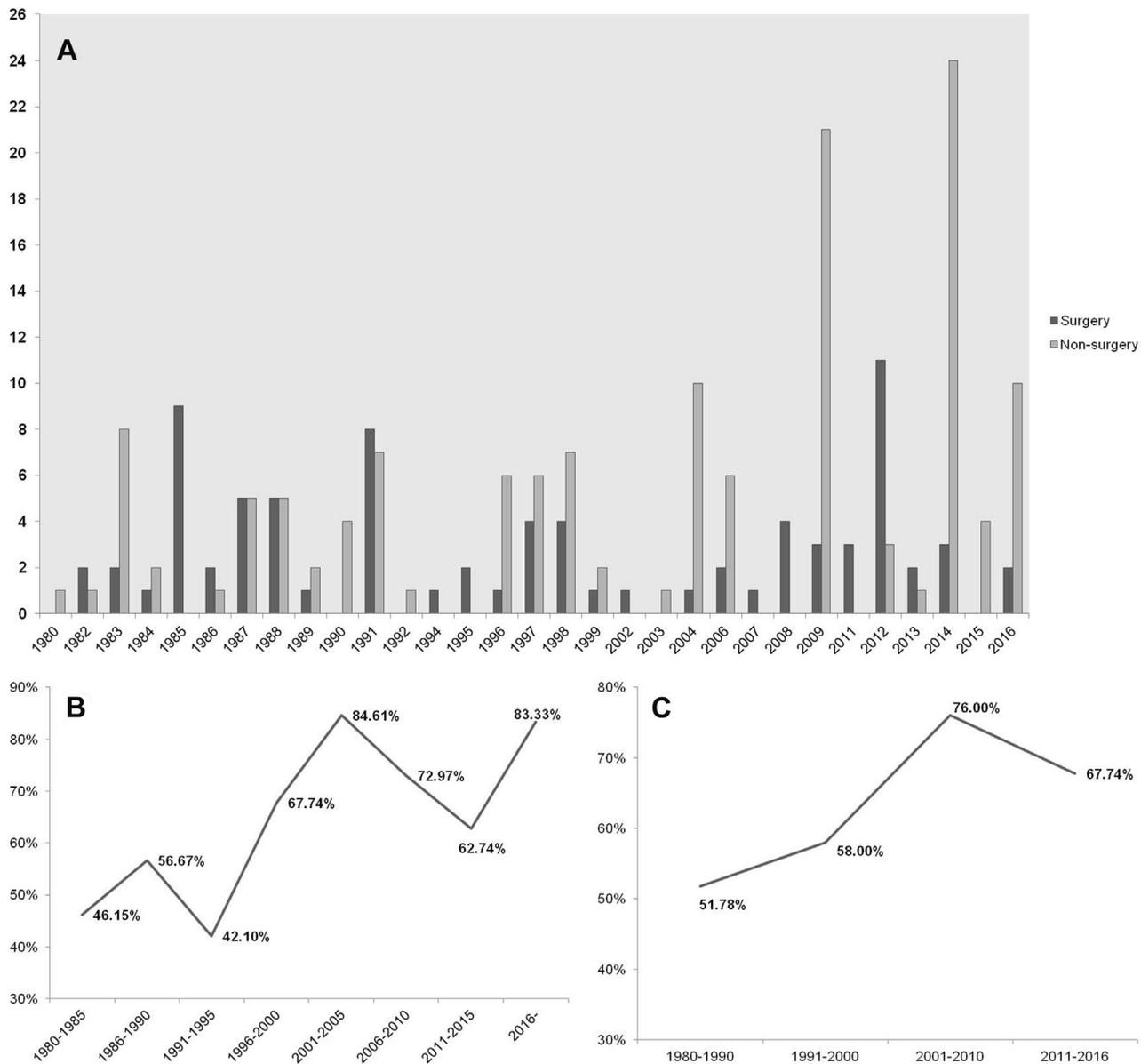
studies of different publication years. [Figure 4, B and C](#) show variations of percentages of nonsurgical cases by time; although differences of such proportions existed among different times, there was a tendency of an increased ratio for conservative treatment for clavicular OM.

## Discussion

Because of the low prevalence of clavicular OM, the number of studies that have reported on this disorder remains limited. Our review, based on pooled outcomes of 294 cases, demonstrated that this disease predominantly affects the female sex and young people. Most patients were in the chronic phase when a definite diagnosis was made, and this was probably because the disease is nonspecific and does not have severe clinical symptoms. The most frequently occurring symptom was pain, with the

medial side of the clavicle being the most frequently involved site. Compared with serum WBC count and CRP values, the ESR may be more helpful because of its higher positive rate before disease management. Most patients achieved favorable outcomes despite surgical or nonsurgical interventions.

Based on different causes, OM can be classified as bacterial or nonbacterial. Compared with the well-defined bacterial OM, the concept of nonbacterial OM is wider. In 1972, Giedion et al<sup>46</sup> first described this clinical entity as CRMO. Later in 1987, Chamot et al<sup>23</sup> first reported SAPHO syndrome, which is characterized by osteoarticular and dermatologic manifestations. Some authors believed that CRMO should be regarded as a pediatric subset of SAPHO syndrome as both share similar characteristics.<sup>57</sup> In addition, some researchers indicated that condensing osteitis and sternoclavicular hyperostosis are special phenotypes of CRMO.<sup>113</sup> Therefore, aside from



**Figure 4** (A) Total numbers of patients managed surgically and nonsurgically among the different publication years. (B and C) Changes in the proportions of patients who received conservative treatment by time.

CRMO, we also included patients with a diagnosis of SAPHO syndrome, condensing osteitis, and sternoclavicular hyperostosis as nonbacterial OM in our analysis. As depicted in Figure 2, clavicle OM was more frequently reported by studies from developed countries, which was probably because of advanced medical technology, increased awareness of this disorder, increased use of technology to diagnose the condition, and increased access to health care in such countries. Our four main findings can be summarized as follows.

First, we noted that clavicular OM predominantly affected the female sex and young people, which was consistent with the results of most published studies. In

a review of CRMO, Taddio et al<sup>109</sup> indicated that CRMO mostly affects children and adolescents, with a female-to-male ratio of 4:1 and an average age at diagnosis of 10 years. Similarly, in a retrospective analysis of 89 patients with nonbacterial osteitis, Jansson et al<sup>57</sup> reported a sex ratio of 1.87 with female predilection and a median age of 10 years at diagnosis. Grote et al<sup>50</sup> compared the clinical characteristics of 378 cases of bacterial OM with 279 cases of nonbacterial osteitis in childhood. They also found a predominance of female sex in nonbacterial osteitis, whereas a predilection of male sex was found in bacterial OM. Therefore, the type of OM may affect the demographics of clavicular OM.

In addition, regional disparity may be another important factor.

Second, we found that 77% of patients were in the chronic phase at diagnosis of clavicular OM, with a median duration of 4 months from the onset of symptoms to diagnosis. These results imply that clavicular OM is a subtle disorder, especially nonbacterial OM.<sup>57,96</sup> In addition, we found that pain is the most frequent clinical symptom, followed by swelling and fever. Clinical manifestations of clavicular OM are highly variable because they are influenced by multiple factors, such as the type of OM, disease phase or stage, and medical interventions. Despite these factors, most symptoms of clavicular OM on presentation were nonspecific and not severe, which might explain the longer interval before a definite diagnosis was made in most cases. In our study, sinus was identified only in patients with bacterial OM (11.67%). Therefore, the diagnosis of bacterial OM can be established once a definite sinus is confirmed. Furthermore, we found that clavicular OM is predominant in the right clavicle (55.84%), mostly with single-site involvement (86.94%). The reason that the right side is more commonly affected remains unclear. Of all the 222 patients with data of the affected site, the medial side of the clavicle, sternoclavicular joint, and medial side plus sternoclavicular joint accounted for the largest percentage (83.33%). Therefore, lesions on the medial side (including the sternoclavicular joint) of the clavicle may strongly imply the possibility of clavicular OM in addition to positive physical examination findings, imaging findings, and laboratory test results.

Third, we observed that positive rates of serum WBC count, ESR, and CRP values were different before treatment, with ESR being first (74.44%), followed by CRP level (40.74%) and WBC count (19.81%). We considered that several factors may influence the positive rate of inflammatory biomarkers before therapy, such as the type of OM, disease course, bacterial virulence, host immune status, and medical intervention. In addition to these external factors, kinetics of the biomarkers including the half-life time during the disease course is the intrinsic factor, which also has a great effect on the positive rate. The half-life times for serologic WBC count, ESR, and CRP level were 6 to 8 hours, 6 weeks, and 18 hours, respectively.<sup>41,78</sup> For example, in the case of bone infection in bacterial OM, the WBC count starts increasing in the first hour and returns to normal after 2 to 3 days in response to treatment. The ESR increases within 1 to 2 days, peaks in 1 week, and takes a much longer time (several weeks) to return to normal. The CRP level begins increasing within 4 to 6 hours, peaks in 48 hours, and returns to normal within 3 to 7 days. Therefore, the ESR is recommended as a follow-up indicator for assessing the efficacy of therapy in patients with OM.<sup>78</sup> With regard to the pathogen culture result, we observed that the positive rate of cultures in patients with bacterial OM was 81.82%, which is significantly higher

than that previously reported in patients with bacterial OM.<sup>58,119</sup> We analyzed a few factors that may affect the positive rate of cultures, such as the culture time, discontinuation of antibiotics before sampling, and culture media. Moreover, we found that *S. aureus* remained the most frequently detected pathogen, which was in accordance with findings of previous studies<sup>58,74,119</sup> of bacterial OM. However, we noted that *M. tuberculosis* (44.70%) was also common (21.18%) in patients with bacterial OM of the clavicle. Therefore, if clinicians suspect clavicular bacterial OM in patients with a negative culture result using a standard culture time and medium, they should consider conducting an extended culture time and medium for *M. tuberculosis*.

Fourth, we found that the average cure rate of clavicular OM was 82.84%, with no statistical difference between surgical and nonsurgical cases. Although indications for surgery or nonsurgery remain a topic of hot debate, there has been a tendency for the proportion of nonsurgical cases to increase in recent years (Fig. 4, B and C), implying acceptable efficacy of conservative treatment of clavicular OM. Deciding between surgery and nonsurgery is usually empirical. For surgical procedures, we observed that débridement with focus curettage was the most commonly used strategy, with a cure rate of approximately 90%. Although total clavicle resection achieved the highest cure rate of 100%, it is not recommended as the first-choice surgical strategy unless the patient has whole clavicle involvement with severe symptoms. Aside from surgery, drug therapy is an important aspect for both bacterial OM and nonbacterial OM of the clavicle. For bacterial OM, sensitive antibiotics are essential. For nonbacterial OM, nonsteroidal anti-inflammatory drugs may be the first-line treatment, with at least 4 weeks of therapy.<sup>76,109</sup> If patients do not respond to nonsteroidal anti-inflammatory drugs, oral corticosteroids (eg, prednisolone) may be another choice as an alternative first-line treatment. Second-line treatment options include bisphosphonates, pamidronate, etanercept, infliximab, and adalimumab.<sup>109</sup>

The study had several limitations. First, although several measures were taken to reduce potential risks of biases (eg, selection bias and publication bias), we could not completely avoid them. Second, the total number of eligible patients was limited, and the majority of the included study types were case reports or cases series. Therefore, considering the limited level of evidence of the study, a cautious attitude should be taken toward the outcomes and conclusions. Last, because both bacterial OM and nonbacterial OM as well as different phenotypes of nonbacterial OM were included in the analysis, heterogeneity may exist in this study. Therefore, future studies should focus on a specific type or phenotype of clavicular OM. Despite these limitations, our study is still valuable as it provides a comprehensive review of the clinical features and treatment of clavicular OM with abundant data. We believe that this

report may help clinicians better recognize and understand clavicular OM.

## Conclusions

Clavicular OM, classified as bacterial or nonbacterial, predominantly affected female patients and young people. The most frequently occurring symptom was pain, with the medial side and sternoclavicular joint of the clavicle the most commonly affected sites. If clavicular OM is suspected, the ESR may be a helpful inflammatory biomarker. Whether a surgery or a non-surgery remedy is chosen, the overall prognosis is good.

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