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ORIGINAL RESEARCH

Similarities and Differences Between Diabetes-Related and Trauma-Related Calcaneal Osteomyelitis: Comparisons Based on 681 Reported Cases

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Background: Current information were still limited regarding clinical characteristics, diagnosis, and treatment efficacy of calcaneal osteomyelitis (CO). The present study summarized similarities and differences between diabetes-related CO (DRCO) and trauma-related CO (TRCO) based on synthesis analysis of literature-reported cases.

Methods: We searched the PubMed, Embase, and Cochrane Library databases to find English studies reporting DRCO and TRCO published between January 2000 and December 2021. Effective data were extracted and synthesized for comparisons.

Results: Altogether 108 studies with 278 DRCO and 403 TRCO patients were analyzed. The ratio of females among the DRCO patients was significantly higher than that of the TRCO patients (37.4% vs 24.3%, $P < 0.001$). The median age at diagnosis of the DRCO patients was statistically older than the TRCO patients (56 vs 44 years, $P < 0.001$). The median symptom duration of the DRCO patients was longer than the TRCO patients (4 vs 2 months, $P = 0.136$), with ulcer and sinus as the top symptoms for the DRCO and TRCO patients, respectively. The positive rate of pathogen culture for the DRCO patients was significantly higher than that for the TRCO patients (94.8% vs 69.5%, $P < 0.001$). The DRCO patients had higher risks of infection relapse (32.3% vs 16.3%, $P < 0.001$) and amputation (24.8% vs 1.4%, $P < 0.001$), and a higher all-cause mortality (4.9% vs 1.3%, $P = 0.03$) than the TRCO patients.

Conclusion: DRCO and TRCO shared similar and different clinical features and diagnostic issues. However, compared with TRCO, the clinical efficacy and prognosis of DRCO were worse.

Keywords: calcaneal osteomyelitis, diabetic foot, post-traumatic osteomyelitis, fracture-related infection, synthesis analysis

Introduction

Calcaneal osteomyelitis (CO), defined as the osseous tissue infection of the calcaneus, represents 3% to 11% of all the bone infections.[1–3] Despite great advances in surgical techniques, currently, successful treatment of CO is still a great challenge as absolute eradication of infection with limb preservation is always difficult. On the one hand, the anatomic location and function of the calcaneus are unique, with limited soft tissue coverage and poor blood supply.[4] In case of infection, such a situation may get even worse, adding the difficulty of treatment. On the other hand, the CO etiology is complex, which often occurs following trauma, orthopaedic surgery, hematogenous spread, and diabetic foot. In addition, pressure sores, nervous

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system problems, and immunosuppression can also lead to CO.[3] Such a wide range of etiology will definitely expand the heterogeneity of this disorder, making it more difficult to treat.[5]

Currently, surgical intervention remains the mainstay of CO treatment. Nonetheless, clinical efficacy is far from satisfying. According to a systematic review,[5] the risk of infection relapse following only bone treatment for CO ranged from 0% to 35%, with the amputation rate ranging from 0% to 29%. The both rates ranged between 0% and 24% even if additional soft tissue coverage was conducted. These data suggest unsatisfactory and poor prognosis of CO. Clinical efficacy of CO is influenced by multiple factors, such as patient age, comorbidities, and the American Society of Anesthesiologists (ASA) score.[4] Among these, etiology is one of the most overlooked factors. A previous study[6] found that patients diagnosed of chronic osteomyelitis (COM) with different etiologies displayed different outcomes of clinical characteristics and diagnostic indicators. This implies that etiology may be an important objective factor that influencing clinical characteristics, diagnosis and even treatment efficacy.

As aforementioned, although the etiology of CO is complex, diabetes and trauma are the top two causes. Diabetes-related CO (DRCO) and trauma-related CO (TRCO) may share similarities and display differences. However, to the best of our knowledge, there still lacks of such studies focusing on comparing DRCO with TRCO. In order to better recognize the two types of CO, we summarized clinical characteristics, diagnosis and treatment efficacy between DRCO and TRCO patients, based on comparisons of literature-reported cases.

Materials and Methods

Literature Search and Study Registration

A literature search was performed by the two independent authors in the PubMed, Embase and Cochrane Library databases to identify English studies reporting clinical characteristics, diagnosis and treatment efficacy of DRCO and TRCO, published between January 1st, 2000 and December 31st, 2021. The following search term was used: "("osteomyelitis" OR "osteitis" OR "bone infection" OR "osteoarticular infection") AND ("calcaneal" OR "calcaneus" OR "heel")". This study protocol had been registered in the PROSPERO database with the registration number CRD42022301091.

Inclusion and Exclusion Criteria

As revealed in Table 1, the PICOS principle was applied to display the detailed inclusion and exclusion criteria.

Study Identification and Data Extraction

Two authors independently screened titles, abstracts, and even full texts to confirm that the recruited studies strictly satisfied the PICOS inclusion criteria. Two authors independently extracted effective data from all the eligible studies. Disagreement was resolved by discussion and when necessary, the corresponding authors' opinion was consulted for final decision.

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) 17.0 software (SPSS Inc., Chicago, IL, USA). Distributions of continuous variables were initially assessed for normality using the Kolmogorov–Smirnov test. Results were presented as mean with range and median with interquartile range (IQR) for normally and abnormally distributed data, respectively. For normally distributed data, Student's *t*-test was used to compare differences between the DRCO and the TRCO patients. Otherwise, the Mann–Whitney test was selected. Dichotomous variables were expressed as percentages with events and totals. The chi-square test was used to compare rate differences between the two groups. A statistically significant difference was defined as a P-value ≤ 0.05.

Results

Study Identification and Characteristics

Altogether 1109 potentially relevant studies were identified initially. After removing the duplicates, screening titles, and evaluating the abstracts and/or the full texts, we finally included 108 studies[7–114] with 681 patients. There were 53 studies

Table 1 Inclusion and Exclusion Criteria of the Current Study: The PICOS Framework

Inclusion Criteria	Exclusion Criteria
Participants (P)	
• Patients diagnosed of DRCO or TRCO • No age limit	• Not DRCO or TRCO (another CO etiologies)
Intervention (I)	
• Surgical or conservative treatment	
Comparison (C)	
• DRCO versus TRCO	
Outcome measures (O)	
• Clinical characteristics: patient sex, age at diagnosis, symptom duration, body side distribution • Diagnosis: clinical symptoms, and pathogen culture outcomes • Treatment strategy and efficacy: treatment methods, infection recurrence and limb amputation following surgical intervention • Prognosis: all-cause mortality	• Studies with unavailable data for synthesis analysis
Study design (S)	
• Randomized controlled trials • Observational studies (cohort studies, case-control studies, case reports/series) • Special article types, including but were not limited to: letters, correspondences, short communications, and meeting abstracts	• Narrative review/summary • Systematic review/Meta-analysis

Abbreviations: DRCO, diabetes-related calcaneal osteomyelitis; TRCO, trauma-related calcaneal osteomyelitis.

reported 278 DRCO cases and 55 studies with 403 TRCO cases, with 4 studies[8,39,44,106] reported DRCO and TRCO at the same time. The eligibility selection process is revealed in Figure 1. The specific data information of the 108 included studies were attached in the supplementary material.

Clinical Characteristics of the Included Patients

Sex Ratio and Age at Diagnosis

Among the included patients, the proportion of females among the DRCO patients was significantly higher than that among the TRCO patients (37.4% vs 24.3%, $P = 0.001$). In addition, the median age at diagnosis of the DRCO patients was significantly older than that of the TRCO patients (56 years vs 44 years, $P < 0.001$) (Table 2).

Infection Duration and Body Side Distribution

The median infection duration of the DRCO patients [median: 4, IQR (2, 6) months] was longer than that of the TRCO patients [median: 2, IQR (1, 8) months], though no statistical difference was found ($P = 0.136$). Also, no statistical difference was found regarding the body side distribution between the two groups of patients (TRCO patients: left: 140, right: 137, bilateral: 1; DRCO patients: left: 23, right: 20, bilateral: 2) ($P = 0.065$) (Table 2).

Clinical Symptoms and Microorganism Culture Outcomes

Local ulcer, wound sinus and pain were top three symptoms for the both DRCO and TRCO patients. However, local ulcer (77.5%) was the most frequently reported symptom for the DRCO patients, while it was wound sinus (52.9%) for the TRCO patients. Significant difference was identified regarding the distributions of clinical symptoms between DRCO and TRCO ($P < 0.001$). To be specific, the proportion of local ulcer was significantly higher, while the percentages of wound

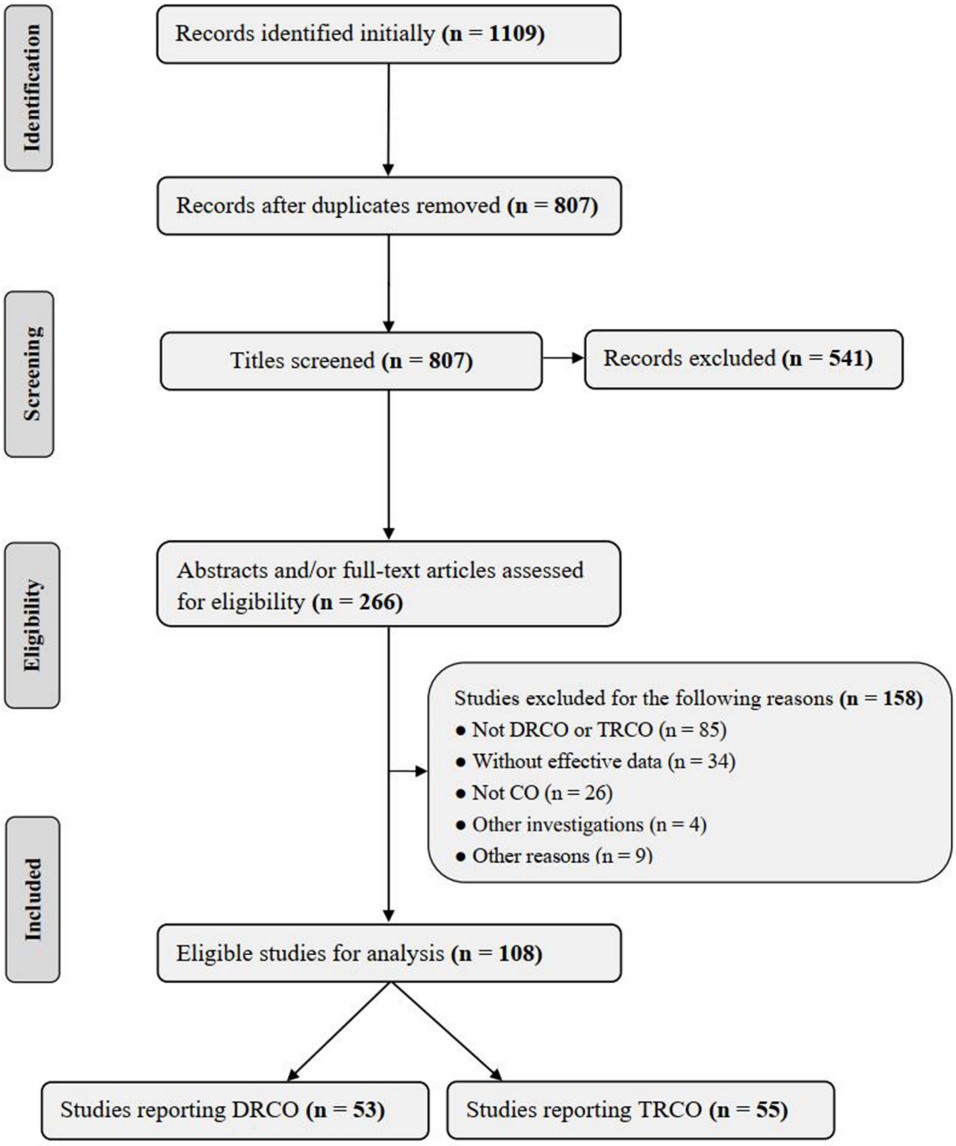

Figure 1 Flow chart of eligibility selection.

sinus, pain, swelling and limited activity were significantly lower among the DRCO patients than those among the TRCO patients ($P < 0.05$) (Table 2).

The positive rate of pathogen culture of the DRCO patients was significantly higher than that of the TRCO patients (94.8% vs 69.5%, $P < 0.001$). In addition, the proportion of polymicrobial infections among the DRCO patients was significantly higher than that among the TRCO patients (34.3% vs 18.4%, $P = 0.029$). Regarding the distributions of detected pathogens for monomicrobial infection, *Staphylococcus aureus* and *Pseudomonas aeruginosa* were the top two for both DRCO and TRCO patients. Distributions of pathogens for the DRCO and TRCO patients were displayed in Figure 2.

Infection Recurrence, Amputation and All-Cause Mortality

The risk of infection recurrence of the DRCO patients following surgical intervention was significantly higher than that of the TRCO patients (32.3% vs 16.3%, $P < 0.001$). In addition, the incidence of limb amputation of the DRCO patients was significantly higher than that of the TRCO patients (24.8% vs 1.4%, $P < 0.001$). Furthermore, the all-cause mortality

Table 2 Similarities and Differences Regarding Clinical Characteristics, Diagnosis, and Treatment Between DRCO and TRCO Patients

Items	DRCO Patients	TRCO Patients	Statistics	*P* values
Sex ratio (F/M)	0.60 (89/149)	0.32 (86/268)	11.731	0.001
Median age at diagnosis (year)	56 (49, 65)*	44 (30.5, 55.5)*	−6.026	<0.001
Symptom duration (month)	4 (2, 6)*	2 (1, 8)*	−1.493	0.136
Side distribution (L/R/B)	23/20/2	140/137/1	/	0.065#
Clinical symptoms	251/45/10/5/5/4/4	48/129/22/16/10/10/9	187.244	<0.001
Ulcer	77.5 (251/324)	19.7 (48/244)	186.496	<0.001
Sinus or exudation	13.9 (45/324)	52.9 (129/244)	99.522	<0.001
Pain	3.1 (10/324)	9.0 (22/244)	9.206	0.002
Swelling	1.5 (5/324)	6.6 (16/244)	9.828	0.002
Redness	1.5 (5/324)	4.1 (10/244)	3.534	0.060
Limited activity	1.2 (4/324)	4.1 (10/244)	4.748	0.029
Edema	1.2 (4/324)	3.7 (9/244)	3.748	0.053
Positive rate of pathogen culture (%) (E/T)	94.8 (109/115)	69.5 (121/174)	27.153	<0.001
Proportion of polymicrobial infection (%) (E/T)	34.3 (24/70)	18.4 (14/76)	4.763	0.029
Infection recurrence rate (%) (E/T)	32.3 (75/232)	16.3 (59/363)	20.959	<0.001
Limb amputation rate (%) (E/T)	24.8 (59/238)	1.4 (3/219)	53.349	<0.001
All-cause mortality (%) (E/T)	4.9 (9/185)	1.3 (3/232)	4.698	0.030

Note: *Data are presented as median with interquartile range.
Abbreviations: DRCO, diabetes-related calcaneal osteomyelitis; TRCO, trauma-related calcaneal osteomyelitis; F/M, females/males; L/R/B, left/right/bilateral; E/T, events/total.

of the DRCO patients was statistically higher than that of the TRCO patients (4.9% vs 1.3%, $P = 0.030$). These outcomes suggest that compared with TRCO, clinical efficacy and prognosis of DRCO were worse.

Discussion

Outcomes of the current study demonstrated that DRCO and TRCO shared both similarities and differences with regard to clinical characteristics, diagnosis and treatment efficacy. Compared with TRCO, DRCO displayed unique features, a higher proportion of female patients, an older median age at diagnosis, a longer median symptom duration. Although local ulcer, wound sinus and pain were the top symptoms for both DRCO and TRCO, local ulcer and wound sinus were

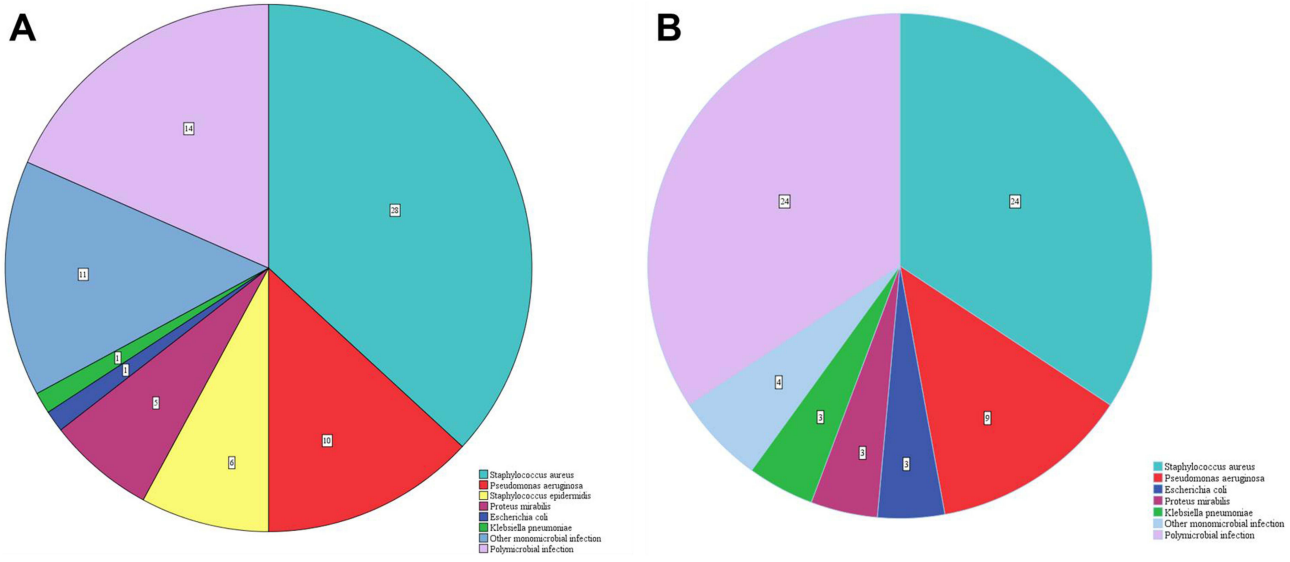

Figure 2 Distributions of the pathogens for DRCO (**A**) and TRCO (**B**).

the most frequently reported symptoms for DRCO and TRCO, respectively. Although the positive rate of culture of DRCO was higher, its efficacy and prognosis were worse, with high incidences of infection relapse, limb amputation, and a higher all-cause mortality, than TRCO. Our findings can be discussed with the following aspects.

First, we found that the proportion of females among the DRCO patients was significantly higher than that among the TRCO patients. Meanwhile, the median age at diagnosis of the DRCO patients was older than that of the TRCO patients. These results were in consistent with our previous study analyzing COM.[6] In that cohort, the ratios of the females patients with diabetic-foot OM (DFOM) and post-traumatic OM (PTOM) were 39.1% and 17.2%, with the median ages at diagnosis being 62 years (DFOM) and 38 years (PTOM), respectively. Among the included studies analyzing TRCO, the investigation with the largest sample size (127 patients) was reported by Huang et al,[15] who summarized clinical features of TRCO. They concluded that young (mean age: 46.8 years) and males (male/female = 4.47) were dominated, which was in line with our results (TRCO: median age: 44 years, male/female = 3.12). Aside from these, the median infection symptom duration of the DRCO patients was longer than that of the TRCO patients. This is probably because diabetes is a chronic disorder, and DROM is classified as vascular insufficiency-related infection.[115,116] These determine that DRCO patients usually experience a long disease term. Quite different from DRCO patients, TRCO patients usually have a wound in the calcaneus before infection occurrence, changes of the wound can be easily noted in case of infection, and thus, the symptom duration of OM is often not long.

Second, we found that the included DRCO and TRCO patients shared similarities and differences in the fields of clinical symptoms and pathogen identification. The top symptoms for both DRCO and TRCO patients were ulcer, sinus and pain. However, the most frequently reported and dominant symptom for DRCO was local ulcer (78%), while sinus was the top among the TRCO patients (53%). The positive rate of culture for DRCO was significantly higher than that for TRCO (95% vs 70%), which revealed similar outcomes with our previous study.[6] In that cohort, the positive rates of culture for DFOM and PTOM patients were 91% and 68%, separately. Regarding potential reasons accounting for such differences between DRCO and TRCO, we considered that it may be linked to the fact that the blood supply to the calcaneus of the DRCO patients may be worse, rendering the antibiotics less effective or even ineffective. Meanwhile, persistent ulcer will definitely increase the detection rate of pathogen. As for the detailed types of pathogens identified, the top two bacteria for both DRCO and TRCO were *Staphylococcus aureus* and *Pseudomonas aeruginosa*, which agrees with previous studies.[6,117] With respect to polymicrobial infection, the percentage of polymicrobial infection of the DRCO patients was statistically higher than that of the TRCO patients, implying the complexity in bacteria species of DRCO.

Third, we found that the treatment efficacy and prognosis of DRCO were worse than TRCO. The overall incidences of infection relapse and limb amputation of the DRCO patients were higher than those of the TRCO patients. Such outcomes may be correlated with several factors. First, the DRCO patients included were relatively older and having diabetes, demonstrating their probably not-so-good immune status. Second, the blood supply to the calcaneus gets even worse in case of infection and diabetes, influencing the efficacy of antibiotics. Third, most of the reported DRCO patients had an ulcer, indicating that the status of their soft tissues was poor. Aside from the above-mentioned factors, infection range, pathogen type and virulence, surgical strategy, and antibiotic selection also affect the treatment efficacy. Previous systematic reviews also analyzed the efficacy of CO. In a 2012 study, Schade VL[118] evaluated the efficacy of partial or total calcanectomy for the management of CO. They concluded that such an alternative strategy to amputation was a viable selection for limb salvage. Later in 2019, Sabater-Martos et al[5] analyzed surgical treatment outcomes of CO among the adult patients. They found that the risks of infection relapse and amputation ranged from 0% to 35% and 0% to 29% among the studies with bone treatment only. Such reinfection and amputation rates ranged from 0% to 24% if additional soft tissue coverage was needed. These outcomes were in consistent with our findings regarding high rates of infection recurrence and limb amputation of the CO patients.

As for mortality, the DRCO patients suffered from a higher risk of all-cause of mortality than the TRCO patients. However, most of the studies did not mention the detailed death causes. One potential reason for such a higher mortality among the DRCO patients rests with the diabetes itself, which not only means a metabolic-related disorder, but also means increased susceptibilities to other system disorders. A previous study[119] found that even COM itself significantly increased the long-term risk of mortality in the elderly. In a recent systematic review and meta-analysis, Yammine et al[120] evaluated the efficacy of partial and total calcanectomies for treatment of diabetic heel ulcers with OM. They found that

the mortality rate of the calcanectomy was as high as 13.4%. In addition, in an observational and retrospective study, Merlet et al[4] analyzed the prognostic factors of CO, and indicated that TRCO is one of the favorable prognostic factors of CO patients. These outcomes support our findings that clinical efficacy and prognosis of DRCO were worse than TRCO.

Our study also has limitations. First, although we included all available studies with different types to lower the risk of selection bias to the minimum, most of the recruited studies were presented as a case report or case series. Thus, the evidence level was not high. Second, the numbers of the DRCO and TRCO patients with available data for analysis were limited, leading to the unavailability of comparisons. Third, we did not evaluate the risk factors for infection recurrence, limb amputation and death, as potentially required data (eg, body mass index, comorbidities, diabetes duration, and detailed surgical strategy with follow-up outcomes) provided by the included studies were also quite limited. Nonetheless, this study provided the useful information on the similarities and differences between DRCO and TRCO, which may help readers better recognize the two types of CO.

Conclusion

In summary, outcomes of the current study demonstrated that, DRCO and TRCO shared similarities and differences regarding clinical characteristics and diagnostic issues. However, compared with TRCO, clinical efficacy and prognosis of DRCO were worse, with higher risks of infection relapse and amputation, and also a higher all-cause mortality. These suggest that DRCO should arouse wide attention and effective preventive measures should be taken to lower the prevalence of DRCO.

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Disclosure

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