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Postoperative complications following orthognathic surgery in patients with rheumatic diseases: A 2-year follow-up study

Keywords: rheumatic diseases; orthognathic surgery; complications; infection

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/odi.14417

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Financial disclosures

The first author was sponsored by the China Scholarship Council (Number 201808510166).

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethical Review Board of the University Hospitals Leuven (reference number: S66025).

Patient consent

Not applicable. As it is a retrospective study, the data are anonymous, and the requirement for informed consent was therefore waived.

Conflict of Interests

The Authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Abstract

Objective

The purpose of this study was to describe the complications following orthognathic surgery in patients with rheumatic diseases and to evaluate rheumatic disease as a possible risk factor.

Methods

A retrospective cohort study was conducted during a 6-year period. The sample consisted of rheumatic and healthy patients who underwent orthognathic surgery. The outcome variables included infection, relapse, respiratory complications, hemorrhage, neurosensory disturbances, temporomandibular joint complications, and removal of osteosynthesis material. Bivariate analysis and logistic regression were applied to identify rheumatic disease as an independent risk factor for complications after orthognathic surgery.

Results

Twenty patients were identified as having rheumatic diseases (male: 2; female: 18; mean age: 37.8 ±13.6 years), and 278 patients were systemically healthy (male: 105; female: 173; mean age: 25.8±11.8 years). The most frequent complications in rheumatic and healthy patients were delayed recovery from neurosensory disturbance (55% and 33%), removal of osteosynthesis material (45% and 26%), and infection (35% and 7%). Following adjustment for possible confounders, rheumatic disease showed a significant association with infection (OR=4.191, p=0.016).

Conclusion

Patients with rheumatic diseases are at a higher risk of postoperative infection following orthognathic surgery compared to healthy patients.

Introduction

Rheumatic diseases cover a wide spectrum of disorders which are primarily characterized by either inflammation, degeneration, or metabolic derangement of connective tissue based

musculoskeletal structures. There are more than 100 distinct conditions labelled as rheumatic diseases. Some of the most representative conditions include rheumatoid arthritis (RA), ankylosing spondylitis (AS), osteoarthritis, fibromyalgia, systemic lupus erythematosus (SLE) and Sjögren's syndrome (Sangha, 2000; Walsh *et al*, 2005; Gabriel and Michaud, 2009). The typical symptoms of these diseases are joint pain, inflammation, and ultimately functional limitation of the affected tissue. In addition, rheumatic patients undergoing surgical interventions are prone to a higher risk of complications and unfavorable prognosis even with an uneventful surgery.(Akkara Veetil and Bongartz, 2012; George and Baker, 2019)

Patients suffering from autoimmune rheumatic diseases, such as RA and SLE, are at an increased risk of infection following orthopedic surgery. (Doran *et al*, 2002; Bongartz *et al*, 2008; Baker and George, 2019) This higher risk might be due to the immunopathogenesis of the disease itself, comorbid conditions, systemic corticosteroid therapy and/or immunosuppressive medications. (Greenberg *et al*, 2010; Liu *et al*, 2013; Mehta *et al*, 2019) Additionally, RA has been also associated with a higher risk of cardiovascular diseases postoperatively due to the presence of elevated inflammatory markers. Another autoimmune disorder known as antiphospholipid syndrome (APS) causes an abnormal production of antiphospholipid antibodies, which leads to an increased risk of blood clot formation and its treatment consists of long-term oral anticoagulation therapy. However, the risk of thromboembolism is transiently increased in patients with APS undergoing surgical procedures due to the temporary interruption of anti-coagulants for achieving an international normalized ratio (INR) of <1.5.(Peters *et al*, 2004; Meune *et al*, 2009; Akkara Veetil and Bongartz, 2012)

Most studies focusing on surgical complications in patients with rheumatic diseases have been conducted following hip or knee joint replacement surgery. To our knowledge, no study exists assessing the risk of complications in such patients after orthognathic surgery. Therefore, the present study aimed to describe the complications following orthognathic surgery in patients with rheumatic diseases and to evaluate rheumatic disease as a possible risk factor. Our hypotheses is that patients with rheumatic diseases will at a higher risk of complications following orthognathic surgery compared to healthy patients.

Materials and Methods

Study design and Patients

This retrospective cohort study was conducted in compliance with the World Medical Association Declaration of Helsinki on medical research. Ethical approval was obtained from the Ethical Review Board of the University Hospitals Leuven (reference number: S66025). Informed consent was not required as patient-specific information was anonymized. The results were reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. (Von Elm *et al*, 2007) The cohort sample consisted of two groups of patients i.e., systemically healthy patients and patients with rheumatic diseases, who underwent orthognathic surgery at the Department of Oral and Maxillofacial Surgery, UZ Leuven, Leuven, Belgium, from April 2013 to May 2019. The inclusion criteria involved patients with a clearly defined malocclusion diagnosis who underwent surgical correction using orthognathic procedures including mandibular (e.g., bilateral sagittal split) and/or maxillary (e.g., Le Fort I) osteotomy with or without genioplasty. Apart from rheumatic diseases, all other systemic diseases were excluded. Pre- and postoperative cone-beam computed tomographic (CBCT) images were acquired for all patients with either Planmeca Promax 3D Max (Planmeca, Helsinki, Finland) or Newtom VGi-evo (Newtom, Verona, Italy) CBCT devices. The scanning parameters were 230 × 260 - 240 × 190 mm2 field of view, 96–110 kV, and a slice thickness of 0.3–0.6 mm. (Shujaat et al, 2022)

All surgeries were executed by a single surgical team and prophylactic antibiotics were administered for approximately 1 week starting on the day of surgery to prevent infection. Patients were systematically administered intraoperative antibiotic prophylaxis at the induction of anesthesia with 1g IV Amoxicillin–Clavulanic Acid or Clindamycin 600mg in penicillin-sensitive patients. The same drugs were continued orally or intravenously till 5 days postoperatively, depending on the patient's feeding condition.

Variables

Medical records of all included patients were reviewed. The recorded baseline variables included: age at the time of surgery (years), gender, type of malocclusion (Angle's classification: class I, II, III based on the mesiodistal relationship between the upper and lower dental arches (Angle, 1899)), orthognathic surgical procedure, intraoperative blood loss (milliliters), operation time (hours), antirheumatic medication, and bone grafting.

All patients were followed up for a period of 2 years. The outcome variables recorded during each follow-up consultation included: wound infection (early- onset: <1 week postoperatively, late-onset: >1 week postoperatively), relapse (clinical diagnosis by the surgeon), respiratory complications (breathing problem requiring additional treatment), and hemorrhage event (severe postoperative bleeding requiring additional treatment during hospitalization or secondary bleeding following hospital discharge). Other postoperative adverse events, such as neurosensory disturbances (hypoesthesia or hyperesthesia of the inferior alveolar nerve and/or infraorbital nerve) and new-onset TMJ complications were only recorded at the end of the 24-month follow-up period because they are normal findings in the early postoperative period in most patients. The neurosensory testing consisted of light touch test with a 5.07/10-g Semmes Weinstein monofilament (Stoelting Co, Wood Dale, IL) and self-reporting by patients.(Agbaje *et al*, 2016) Furthermore, pain and thermal testing were performed using sharp pin and a cold tuning fork, respectively. The sensory feedback was categorized as normal, hypoesthesia, hyperesthesia, or slightly diminished sensation. Patients with positive sensory outcomes such as paresthesia, dysesthesia, and pain were categorized as 'hyperesthesia', while patients with negative outcomes were classified as 'hypoesthesia'. (Politis *et al*, 2013) The final diagnosis was based on patient history, physical examination and sensory testing as suggested by Gilron et al. (Gilron *et al*, 2006) TMJ complications included TMJ pain (spontaneous pain or pain elicited by local pressure, eating, speaking in face, jaw joint area, and in or around the ear), TMJ sound (clicking, popping or grating sound coming from the TMJ when opening or closing the mouth), non-linear opening path, and limited mouth opening (maximal interincisal opening of 35mm or less). The need for removal of osteosynthesis material was recorded because reasons for removal included infection, pain and irritation, and local sensory changes on the skin.

Statistical analysis

Data were analyzed using SPSS statistical software (version 22.0; IBM, Armonk, NY, USA). Baseline and outcome variables were compared between the study groups using Mann-Whitney test for continuous, and Pearson's chi-square or Fisher's exact test for categorical variables. Univariable logistic regression was used to evaluate the crude association between patients with rheumatic diseases and the recorded outcomes. Multivariable logistic regression was used to assess rheumatic disease as an independent risk factor for all recorded outcomes. Baseline variables were included in the multivariable model if bivariate analysis showed a P-value of <0.05 for the association with each outcome. Multicollinearity between variables

was evaluated using the variance inflation factor (VIF). For all comparisons between baseline variables, VIF was less than 5 indicating no multicollinearity was present. A P-value of < 0.05 was considered statistically significant. Complete-case analysis was used in our study.

Results

Figure 1 illustrates the flowchart of the patient selection process. A total of 886 patients underwent orthognathic surgery over a period of 6 years. Following inclusion and exclusion criteria, 20 patients were identified as having rheumatic diseases (male: 2; female: 18; mean age: 37.8 ±13.6 years), and 278 patients were systemically healthy (male: 105; female: 173; mean age: 25.8±11.8 years). In total, nine types of rheumatic diseases were identified, which also included a patient with both RA and fibromyalgia, and another patient with osteoporosis and fibromyalgia. Additionally, nine patients suffered from a rheumatic disease in combination with another systemic disease, which included asthma (n=4), Ehlers-Danlos syndrome (n=1), diabetes mellitus type 1 (n=2), hypothyroidism (n=1) and hyperthyroidism (n=1). Table 1 describes the baseline characteristics of the included patients. The patients in the rheumatic group were significantly older than those in the healthy group ($p<0.001$, Mann-Whitney U test). The mean blood loss in the rheumatic and control group was 181.7 ml and 173.1 ml and the mean operation time was 2.4 h and 2.1 h, respectively. In addition, no significant difference existed between both groups in relation to either blood loss (P=0.783) or operative time (P= 0.692).

In 30% (6/20) of rheumatic patients at least one antirheumatic drug was administered before surgery, which included Methotrexate, Etanercept and Adalimumab. Drug holiday varied depending on the administered drugs, where Methotrexate, Etanercept and Adalimumab were discontinued 2 weeks to 1 month before the surgery and restarted when the surgical wounds had healed. In addition, these patients also received minocycline, glucosamine and curcumin starting from 3 months preoperatively till 3 months following surgery. (Brijs *et al*, 2022)

A comparison of the outcome variables between the study groups is depicted in Table 2. One or more complications were reported by 90% and 63% rheumatic and healthy patients, respectively. At the end of 2-year follow-up period, the most frequent complication in rheumatic and healthy patients was delayed recovery from neurosensory disturbance (55% (11/20) and 33% (92/278)), followed by removal of osteosynthesis material (45% (9/20) and 26% (72/278)), TMJ complications (30% (6/20) and 29% (80/278)) and infection (35% (7/20) and 7% (19/278)). The risk of infection (p=0.001, Fisher's exact test), neurosensory

disturbance (p=0.047, Chi-squared test) and TMJ pain (p=0.049, Fisher's exact test) was significantly higher in patients with rheumatic diseases compared to healthy patients. In rheumatic group, only 1 patient suffered from early-onset infection, while 6 patients had late-onset infection (mean: 4.9 months, range: 6 weeks - 1 year). On the contrary, the patients in healthy group (n=19) only had late-onset infection (mean: 6.2 months, range: 2 weeks - 2 years). There was a significant difference in onset of infection between the study groups (Log-rank p-value <0.001), as displayed in Figure 2.

Logistic regression analysis was used to control for confounders of the association between rheumatic diseases and recorded outcomes (Table 3). Compared to healthy patients, the risk of infection (adjusted OR=4.191 [1.313, 13.380], P=0.016) was increased in patients with rheumatic diseases. In the rheumatic group, there was no link between prescribed anti-rheumatic drugs and postoperative infection (P=0.290, Fisher's exact test).

Discussion

The purpose of this study was to describe the complications following orthognathic surgery in patients with rheumatic diseases and to identify possible risk factors. Following adjustment for confounding variables, rheumatic diseases only showed an increased risk of infection. Our result suggesting a higher risk of postoperative infection in patients with rheumatic diseases is consistent with the evidence based on hip and knee orthopedic surgical procedures. (Doran *et al*, 2002; Bongartz *et al*, 2008; Baker and George, 2019) This might be attributed to the immunological alterations by the disease itself, which has been confirmed in several studies where a higher risk of infection exists in rheumatic patients compared to the general population. Other reasons include medical therapy used to treat the diseases such as biological agents, disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids. (Greenberg et al, 2010; Liu et al, 2013; Mehta et al, 2019) In our study, however, no relationship existed between the prescribed anti-rheumatic drugs and postoperative infection in rheumatic group. Additionally, most infections occurred after the perioperative period, which are not expected to be influenced by the perioperative medical management. Current surgical practice supports continuing conventional synthetic DMARDs (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, doxycycline) and SLE-specific medications perioperatively. (Goodman and George, 2020) For biologic agents, it is better to stop taking the drugs prior to surgery and scheduling the surgery at the end of the dose cycle. Thereafter,

the medications should be resumed at a minimum period of 14 days following surgery in the absence of wound healing problems, surgical site infection, or systemic infection. (Ronald MacKenzie et al, 2018) Furthermore, most rheumatic patients included in the study had at least one comorbid condition and belonged to an older age group, both of which have been known to significantly contribute towards infection. These diseases cause impairment of the immune system's ability to respond to novel antigenic stimuli. (Doran et al, 2002) However, the pathophysiology of rheumatic diseases is complicated involving interaction of genetic, hormonal, environmental, and immunologic factors. (Joseph et al, 2010) Thereby, requiring future investigations to clarify the relationship between these factors and postoperative complications.

The risk of surgical relapse was relatively low without any significant association with rheumatic diseases, which was consistent with previous studies. (Thaller et al, 1990; Leshem et al, 2006; Pagnoni et al, 2013) At the same instance, some studies have shown a higher amount of relapse ranging 21% to 48% following BSSO mandibular advancement in patients with juvenile idiopathic arthritis who also suffered from resorptive TMJ disorders. (Oye et al, 2003; Stoor et al, 2018) This conflicting evidence in relation to surgical stability in patients with inflammatory rheumatic diseases could be dependent on the severity and progression of the disease. Hence, it is recommended to perform orthognathic surgery in patients with TMJ arthritis only when the disease process has stabilized, or when the disease severity is mild or quiescent with relatively modest abnormalities for achieving a stable outcome. (Covert *et al*, 2021) Further, three-dimensional CBCT-based studies are warranted to objectively assess TMJ changes with a matched case-control group, as the present study only focused on providing a more descriptive approach towards complications in rhematic patients.

Although the present study did not show a high risk between rheumatic diseases and postoperative TMJ pain, it is well known that TMJ can be involved in patients with rheumatic disease. In a matched case-control study, Helenius et al. reported significantly severe clinical and radiological TMJ symptoms in patients with rheumatic diseases compared to the control group. (Helenius *et al*, 2005) It should be noted that rheumatic patients with preexisting TMJ dysfunction who are planned to undergo orthognathic surgery, particularly mandibular advancement, are more likely to suffer from extensive exacerbation of postoperative TMJ symptoms. Therefore, it is crucial to closely monitor these symptoms and any dysfunction should be surgically addressed separately or concomitantly with orthognathic surgery if

necessary where conservative management fails to resolve the issue at hand. (Wolford *et al*, 2003) In present study, rheumatic disease was in remission before surgery, which is the most favorable period for such an intervention. In addition, no systemic symptoms were found in our group of patients. Future prospective studies are warranted to assess the relationship between systemic symptoms and post-surgical complications.

The current study had certain limitations. First, the findings should be interpreted with caution due to the retrospective design and limited sample size of patients with rheumatic diseases. Second, the complications also rely on the severity and control of the disease, variables which were not recorded. Third, residual confounding may influence several important outcomes, such as the effect of smoking and comorbid conditions on infection. Hence, future investigations should record these additional variables for a more objective reporting of the complications.

Conclusion

Patients with rheumatic diseases are at a higher risk of postoperative infection following orthognathic surgery compared to healthy patients. The implications of both the complications per se and their treatment should be taken into consideration when planning orthognathic surgical procedures, specifically in relation to post-operative infection, TMJ pain and neurosensory disturbances which are higher in rheumatic patients. As for the medico-legal implications, patients should also be well informed of the increased risk of complications. Furthermore, practice guidelines for peri- and post-operative management of these patients should be established based on detailed recordings of complications and their confounders.

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Table 1. Baseline Characteristics of healthy and rheumatic patients.

Characteristics	Patients with rheumatic diseases (n=20)	Patients without systemic diseases (n=278)	P-value
Age, mean (SD), year	37.8 (13.6)	25.8 (11.8)	<0.001 [a]
Female, n (%)	18 (90.0)	173 (62.2)	0.012 [b]
Type of malocclusion, n (%)			0.317 [b]
Class I	0 (0.0)	2 (0.7)	
Class II	17 (85.0)	192 (69.1)	
Class III	3 (15.0)	84 (30.2)	
Type of surgery, n (%)			0.606 [b]
Bimax	9 (45.0)	125 (45.0)	
mandibular	8 (40.0)	129 (46.4)	
maxilla	3 (15.0)	24 (8.6)	
Blood loss, mean (SD), ml	181.7 (163.2)	173.1 (112.2)	0.783 [a]
Operation time, mean (SD), h	2.4 (2.2)	2.1 (0.9)	0.692 [a]
Bone grafting, n (%)	9 (45.0)	77 (27.7)	0.990 [b]
Antirheumatic drugs, n (%)	6 (30.0)	0 (0)	/

[a] P-value of Mann-Whitney U test; [b] P-value of Chi-square test.

SD: standard deviation; Bimax, bimaxillary osteotomy, including mandibular and maxillary osteotomy.

Table 2. Risk of postoperative outcomes in healthy and rheumatic patients.

Complications	Patients with rheumatic diseases (n=20)	Patients without systemic diseases (n=278)	*P*-value
Total, n (%)	18 (90.0)	175 (62.9)	**0.001** [a]
Infection, n (%)	7 (35.0)	19 (6.8)	**0.001** [a]
Removal osteosynthesis material, n (%)	9 (45.0)	72 (25.9)	0.064 [b]
Relapse, n (%)	1 (5.0)	13 (4.7)	>0.999 [a]
Neurosensory disturbance, n (%)	11 (55.0)	92 (33.1)	**0.047** [b]
Temporomandibular joint (TMJ) complications, n (%)			
TMJ pain	4 (15.0)	18 (6.5)	**0.049** [a]
TMJ sound	1 (5.0)	44 (15.8)	0.330 [a]
Non-linear opening path	1 (5.0)	34 (12.2)	0.487 [a]
Limited mouth opening	0 (0)	12 (4.3)	>0.999 [a]
Total	6 (30.0)	80 (28.8)	0.907
Bleeding-related complications, n (%)	0 (0)	3 (1.1)	>0.999 [a]
Respiratory complications, n (%)	0 (0)	2 (0.7)	>0.999 [a]

[a] P-value of Fisher's exact test; [b] P-value of Chi-squared test.

Table 3. Odds ratios (direct effects) of all outcomes for patients with versus without rheumatic diseases.

Outcome	Unadjusted OR [95% CI]	P	Adjusted OR [95% CI] *	P
Infection	7.340 [2.620, 20.564]	**0.000**	4.191 [1.313, 13.380]	**0.016**
Removal of material	2.341 [0.932, 5.879]	0.070	1.451 [0.548, 3.842]	0.453
Relapse	1.073 [0.133, 8.644]	0.947	0.136 [0.001, 28.547]	0.465
Neurosensory disturbance	2.471 [0.989, 6.174]	0.053	1.085 [0.383, 3.076]	0.878
TMJ complains	1.061 [0.394, 2.857]	0.907	0.895 [0.328, 2.446]	0.829
Bleeding-related complications	N/A	N/A	N/A	N/A
Respiratory complications	N/A	N/A	N/A	N/A

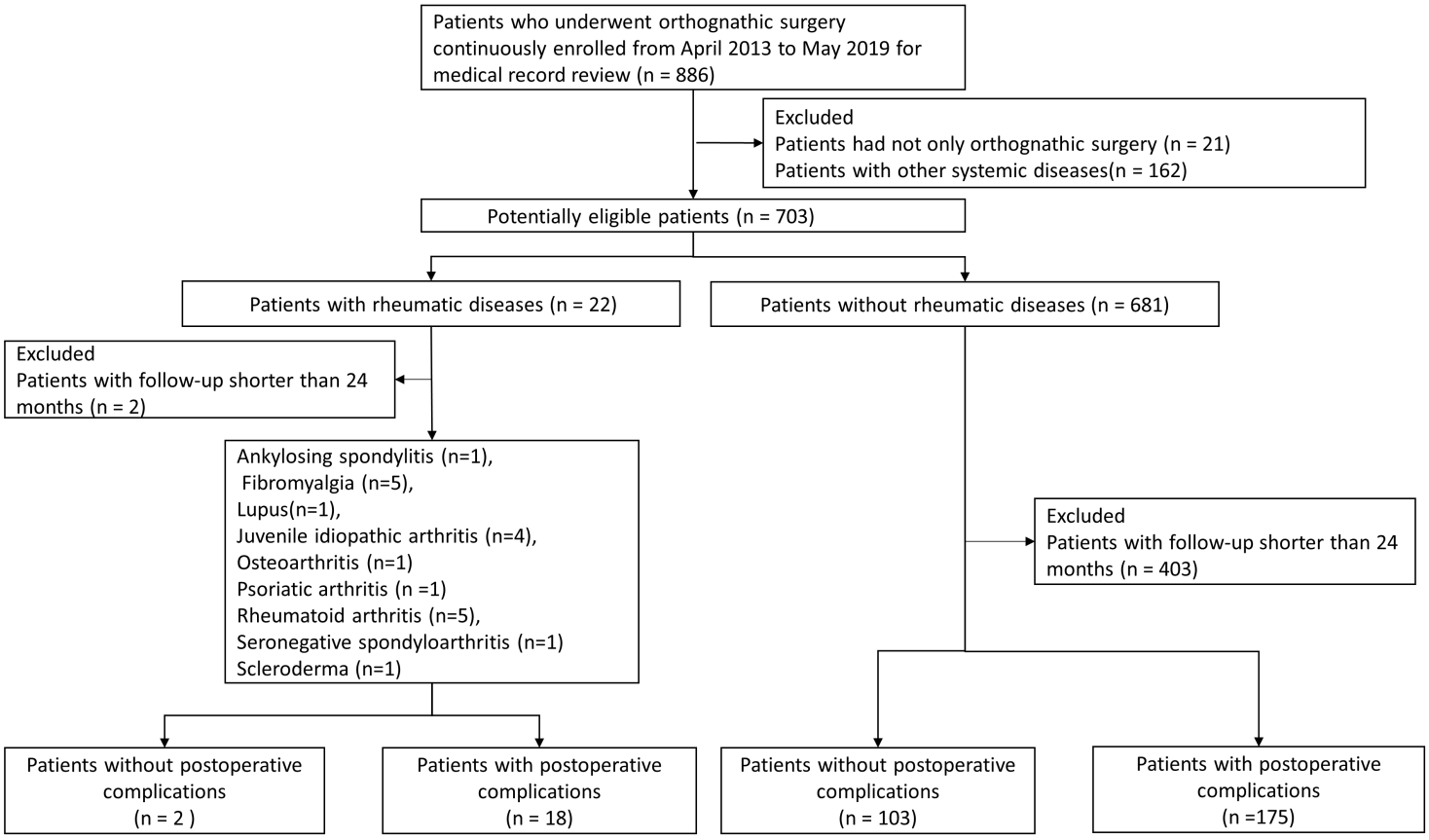
* Adjusted models for infection include age, gender and operation time. Adjusted models for removal of material include gender, age, and blood loss. Adjusted models for relapse type of surgery, blood loss, operation time, and grafting. Adjusted models for neurosensory disturbance include age. Adjusted models for TMJ complains include gender and malocclusion.

N/A: not applicable due to lack of samples.

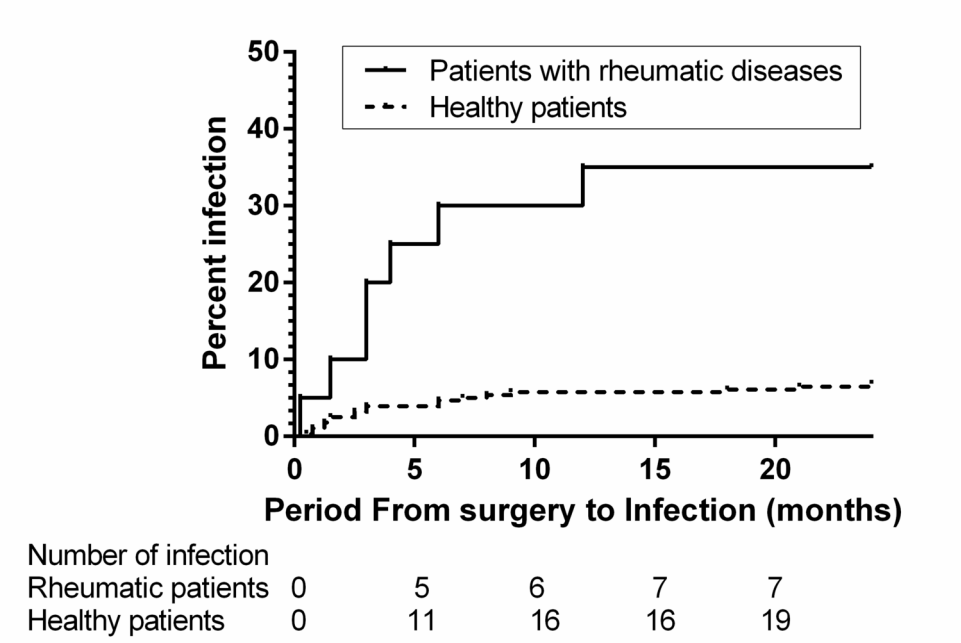
Figure Legend

Figure 1. Flowchart of patient selection process.

Figure 2. Kaplan-Meier curve for period from surgery till infection (Log-rank $p < 0.0001$).



ODI_14417_Figure 1. Flowchart of patient selection process.tif



ODI_14417_Figure 2. Kaplan-Meier curve for months from surgery to infection.tif