OMFS IMPATH

KU Leuven
Biomedical Sciences Group
Faculty of Medicine
Department of Imaging & Pathology
OMFS-IMPATH Research Group
Kapucijnenvoer 7 block a - box 7001
B-3000 LEUVEN, BELGIUM
jiqing.li@kuleuven.be

The author

Jiqing Li achieved her degree in Bachelor of Dental Medicine from School of Stomatology, Shandong University, Jinan, China (2009-2014). She obtained her “Master of Dental Medicine” degree from West China College of Stomatology, Sichuan University, Chengdu, Sichuan, China (2014 - 2017). After her graduation, she worked as a general dentist at West China Hospital of Stomatology, Chengdu, China (2017-2018). She started working as a Ph.D. candidate (OMFS-IMPATH, KU Leuven) in 2018, with Prof. Reinhilde Jacobs, Prof. Constantinus Politis, and Dr. Eman Shaheen as her (co-)promotors.

Abstract

This doctoral thesis investigates the impact of systemic diseases on orthognathic surgery outcomes, aiming to enhance treatment approaches. Through prevalence studies and retrospective cohort analyses, the research reveals distinct complications associated with conditions such as rheumatic diseases, osteopenia, myotonic dystrophy, congenital myopathy, asthma, and autoimmune diseases. These findings offer valuable insights into the challenges and considerations when treating orthognathic surgery patients with systemic diseases. Ultimately, this work contributes to the advancement of patient care and surgical strategies in this specialized context.

Jiqing Li

EVALUATION OF POSTOPERATIVE OUTCOMES IN ORTHOGNATHIC SURGERY PATIENTS WITH SYSTEMIC DISEASES

Oct 2023

KU LEUVEN

DOCTORAL SCHOOL of BIOMEDICAL SCIENCES

Evaluation of Postoperative Outcomes in Orthognathic Surgery Patients with Systemic Diseases

JIQING LI

Supervisor:
Prof. dr. Reinhilde Jacobs
Co-supervisor:
Prof. dr. Constantinus Politis
Dr. ir. Eman Shaheen

Dissertation presented in partial fulfillment of the requirements for the degree of Doctor in Biomedical Sciences

Oct 2023

KU Leuven
Biomedical Sciences Group
Faculty of Medicine
Department of Imaging and Pathology

DOCTORAL SCHOOL
BIOMEDICAL SCIENCES

EVALUATION OF POSTOPERATIVE OUTCOMES IN ORTHOGNATHIC SURGERY PATIENTS WITH SYSTEMIC DISEASES

Jiqing Li

Dissertation presented in partial fulfilment of the requirements for the degree of Doctor in Biomedical Sciences

Jury:

Supervisor: Prof. dr. Reinhilde Jacobs
Co-supervisor: Prof. dr. Constantinus Politis
Dr. ir. Eman Shaheen
Chair examining committee: Prof. dr. Tatiana Kouznetsova
Chair public defence: Prof. dr. Tania Roskams
Jury members: Prof. dr. Antoon De Laat
Prof. dr. Andy Temmerman
Prof. dr. Nasser Alqhtani
Prof. dr. Krisztian Nagy

July 2023

Preface

This doctoral thesis consists of 5 research articles, preceded by a general introduction and concluded with a general discussion. The research articles followed the standard scientific IMRAD structure (Introduction, Materials and Methods, Results and Discussion) and were based on the following peer-reviewed publications:

Article 1

J. Ver Berne, **J. Li**, E. Shaheen, C. Politis, H. Peeters, R. Jacobs. Prevalence and characteristics of systemic conditions in patients undergoing orthognathic surgery: a retrospective study. *International Journal of Oral and Maxillofacial Surgery*. 51 (9):1205-1210 (2022). https://doi.org/10.1016/j.ijom.2022.02.004

Article 2

J. Ver Berne, C. Politis, J. Meyns, **J. Li**, R. Jacobs. Prevalence of systemic conditions in an orthognathic surgery population: a 20-year single-center study. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology.* 134(2):163-167 (2022). https://doi.org/10.1016/j.oooo.2022.01.003.

Article 3

J. Li, S. Shujaat, J. Ver Berne, E. Shaheen, Wim Coucke, C. Politis, R. Jacobs. Post-operative complications following orthognathic surgery in patients with rheumatic diseases: A 2-year follow-up study. *Oral diseases*. (2022) Epub ahead of print. https://doi.org/10.1111/odi.14417

Article 4

J. Li, S. Shujaat, E. Shaheen, J. Ver Berne, C. Politis, R. Jacobs. Postoperative complications in asthmatic patients following orthognathic surgery： A two-year follow-up study. *Journal of Stomatology, Oral and Maxillofacial Surgery*, 124(3):101388 (2023). https://doi.org/10.1016/j.jormas.2023.101388

Article 5

J. Li, S. Shujaat, E. Shaheen, C. Politis, R. Jacobs. Autoimmune diseases and orthognathic surgery: a case series of 12 patients. *Journal of plastic, reconstructive & aesthetic surgery*. 84：413-421 (2023). https://doi.org/10.1016/j.bjps.2023.06.017

Personal Acknowledgements

First and foremost, I would like to convey my gratitude to my supervisor, **Prof. Reinhilde Jacobs**. I am very grateful for her help, encouragement, and patience throughout my Ph.D. years. I could not have completed my Ph.D. without her support.

Second, I'd like to sincerely thank **Prof. Constantinus Politis** and **Dr. Eman Shaheen**, my co-promoters. Throughout my Ph.D., they have provided me with unwavering care and support in both my academics and life. They have been excellent role models for me to learn from.

In particular, I wish to express my deep gratitude to my colleagues, **Dr. Sohaib Shujaat** and **Dr. Jonas Ver Berne**. I greatly acknowledge their support and assistance during my Ph.D. They are both good friends and great teachers.

Furthermore, I would like to express my sincere gratitude to **Prof. Antoon De Laat** and **Prof. Andy Temmerman** for their invaluable support throughout my entire Ph.D. journey. Their guidance and mentorship have been instrumental in my academic growth. I would also like to extend my appreciation to **Prof. Nasser Alqhtani** from Prince Sattam bin Abdulaziz University and **Prof. Krisztian Nagy** from Semmelweis University for their assistance and contributions. Your support has played a significant role in the gradual completion of my academic work, and I am truly grateful to each one of you.

In addition, I'd like to express my gratitude to the entire **OMFS-IMPATH research group**. I have lovely memories of the welcoming and helpful work environment. Especially to my friends from **Rudra**, your friendship helped me cope with the loneliness of studying abroad.

Most of all, I would like to thank my parents (**Yong & Yuping**), my husband (**Meng**), and my son (**Fubao**). Without your love and support, I would never have been able to finish my Ph.D. study abroad. I sincerely hope that I can make you proud.

Also, thanks to my motherland and the China Scholarship Council (CSC). Despite the challenges posed by the COVID-19 pandemic, they have supported me in completing my studies. I hope that I can dedicate my strength to the development of my motherland.

Table of Contents

List of Abbreviations

2D	Two-dimensional
3D	Three-dimensional
ADHD	Attention deficit and hyperactivity disorder
APS	Antiphospholipid syndrome
AS	Ankylosing spondylitis
Bimax	Bimaxillary osteotomy
BMI	Body mass index
BSSO	Bilateral sagittal split osteotomy
CBCT	Cone-beam computed tomography
COPD	Chronic obstructive pulmonary disorder
DFD	Dentofacial deformity
DM	Diabetes mellitus
DMARD	Disease-modifying anti-rheumatic drugs
EVRO	Extra-oral vertical ramus osteotomy
FGF	Fibroblast growth factor
INR	International normalized ratio
IVRO	Intraoral vertical ramus osteotomy
JIA	Juvenile idiopathic arthritis
JRA	Juvenile rheumatoid arthritis
LF I	Le Fort I osteotomy
LLLT	Low-level laser therapy
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds ratios
OSA	Obstructive sleep apnea
RA	Rheumatoid arthritis
SARPE	Surgically assisted rapid palatal expansion
SLE	Systemic lupus erythematosus
SSI	Surgical site infection
SSO	Sagittal split osteotomy
SSRO	Sagittal split ramus osteotomy
TBT	Template bleeding time
TMJ	Temporomandibular joint
TMDs	Temporomandibular joint disorders

General Introduction

Aims & Hypotheses

0.1 Systemic diseases

0.1.1 Brief introduction of systemic diseases

Systemic diseases, also referred to as systemic disorders or systemic illnesses, encompass medical conditions that affect multiple organ systems or the entire body, as opposed to being localized to a specific organ or body part. For instance, diabetes mellitus is a metabolic condition marked by elevated levels of blood sugar due to insufficient production of insulin (Type 1 diabetes) or the body's resistance to insulin (Type 2 diabetes). It impacts various systems, including the cardiovascular, nervous, renal, and ocular systems [1]. Another example is Crohn's disease, an inflammatory bowel disease that causes chronic inflammation within the gastrointestinal tract. It may affect any part of the gastrointestinal tract, leading to symptoms such as abdominal pain, diarrhea, weight loss, and nutritional deficiencies [2]. Multiple sclerosis is an autoimmune disorder characterized by the immune system mistakenly attacking the protective coating of nerve fibers in the central nervous system. This condition presents a diverse array of symptoms, such as muscle weakness, fatigue, coordination difficulties, and cognitive impairment [3]. Rheumatoid arthritis (RA), another autoimmune disorder, primarily affects the joints, resulting in chronic inflammation, pain, stiffness, and joint deformity. Moreover, it can also impact other organs, such as the heart, lungs, eyes, and blood vessels [4].

The development of systemic diseases can be attributed to a multitude of factors, including genetic predisposition, infections, autoimmune disorders, metabolic abnormalities, environmental factors, and lifestyle choices [5]. These diseases might progress over time and often remain hidden. However, their effects are extensive, leading to inflammation, organ dysfunction, and complications. In particular, individuals with chronic systemic inflammatory diseases, such as systemic lupus erythematosus (SLE), RA, ankylosing spondylitis (AS), and multiple sclerosis, face significant challenges due to long-lasting debilitating symptoms, increased mortality rates, and high costs associated with medical care and treatment [6].

Systemic diseases often require comprehensive management involving a team of healthcare professionals, including specialists in rheumatology, endocrinology, gastroenterology, or infectious diseases. To manage symptoms, prevent complications, and enhance overall quality of life, treatment approaches may involve medication, physical therapy, lifestyle modifications, and ongoing monitoring.

0.1.2 Impact of systemic diseases on postoperative complications

Patients with systemic diseases who undergo surgery might face unique considerations and potential challenges during their intraoperative and postoperative recovery. The interaction between the surgical procedure and systemic disease may increase the risk of complications and affect the overall outcome. This introduction aims to explore the effects of various prevalent systemic diseases in this context.

0.1.2.1 Cardiovascular diseases

Cardiovascular diseases (CVD) encompass a range of conditions that affect the heart and blood vessels. The causes of CVD are multifaceted, with some risk factors being modifiable through lifestyle changes and medications. These risk factors include high blood pressure, hypercholesterolemia, obesity, diabetes, unhealthy diet, stress, tobacco consumption, and physical inactivity [7]. Conversely, certain risk factors such as advanced age, inherited disposition, gender, and ethnicity are nonmodifiable [8]. During the perioperative period, cardiac complications resulting from non-cardiac surgeries impose a substantial burden in terms of both mortality as well as morbidity.

Hypertension has the potential to contribute to the development of coronary artery disease, cardiomegaly, congestive heart failure, and organ damage in critical areas such as the kidneys, heart, retina, and brain. Individuals with hypertension are at an elevated risk of experiencing significant hypotensive episodes when exposed to sedative and anesthetic agents due to heightened peripheral vascular resistance. Prolonged excessive hypotension, resulting from attempts to lower blood pressure, might be more harmful during surgery in patients with significant peripheral vascular disease than tolerating moderate hypertension [9]. Although administering acute hypertension treatment during elective surgery might provide temporary reassurance to the practitioner, it could lead to significant blood pressure fluctuations, which in turn could increase the risk of morbidity or mortality [10].

0.1.2.2 Pulmonary diseases

Patients with upper respiratory diseases should wait for at least two weeks after their symptoms start to improve before undergoing elective surgery. According to a recent study, 10% of cases were associated with severe complications such as respiratory and cardiac arrest, pneumonia, and prolonged intubation. These complications were linked to increased sputum production [11].

Emphysema and chronic bronchitis are two disorders that are part of chronic obstructive pulmonary disease (COPD), leading to airflow blockage and respiratory difficulties. Surgical procedures and anesthesia generally pose minimal intraoperative risks for patients with significant COPD, considering the nature of the lung disease. However, individuals with COPD experience a markedly high risk of postoperative pulmonary problems [12].

In contrast to the general population, previous research has shown that asthmatic patients undergoing surgery are more likely to experience sepsis, postoperative pulmonary problems, urinary tract infection, and consequent mortality [13]. This increased risk of airway-related infections is strongly connected to impaired innate and adaptive immune functions and peripheral blood eosinophilia. Furthermore, individuals with neutrophilic airway inflammation tend to have elevated levels of systemic inflammation, which may negatively impact their clinical outcomes. This inflammation is caused by increased levels of proinflammatory cytokines and immune cells in the bloodstream [14]. Moreover, certain medications used during the perioperative period, such as atracurium and mivacurium, have been associated with pulmonary complications. These medications have the potential to trigger allergic reactions by releasing histamine, which may exacerbate respiratory symptoms [15].

Smoking is widely recognized to increase the risk of wound infection. Even in smokers without chronic lung disease, it could raise carboxyhemoglobin levels, impair ciliary function, and increase sputum production. Quitting smoking for just two days could reverse these effects. However, a minimum cessation period of 8 weeks is needed to reduce postoperative pulmonary complications [16]. Administering a bronchodilator, such as fluticasone, prior to surgery could help alleviate the increased airway reactivity commonly observed in smokers under general anesthesia [17].

0.1.2.3 Hematologic diseases

The most common hematologic condition is anemia, which is defined by a decrease in red blood cell formation. Abnormal bleeding associated with anemia could lead to edema, thereby increasing the risk of postoperative infection. Moreover, long-term anemia could negatively impact bone maturation and development. Specifically, there is typically a reduction of 25% to 40% in the trabecular pattern [18]. These factors could potentially influence the long-term outcomes of bone surgeries.

Thalassemia, an inherited hematologic disorder, arises from mutations affecting the synthesis of hemoglobin [19]. Thalassemic patients have a higher risk of bleeding and are more susceptible to infection [20,21]. In addition to thalassemia, other genetic diseases such as von Willebrand's disease (autosomal dominant transmission), hemophilia A and B (sex-linked recessive inheritance), and liver disease may also lead to bleeding problems [12].

0.1.2.4 Rheumatic diseases and autoimmune diseases

Patients with rheumatic conditions who undergo surgical interventions are more susceptible to an increased risk of complications and unfavorable outcomes [22]. Recent studies suggest that individuals suffering from autoimmune rheumatic disorders are more susceptible to infections following surgery. The majority of this evidence is derived from studies focusing on joint replacement surgeries [23]. Additionally, multiple studies have identified an elevated cardiovascular risk associated with various rheumatic diseases. Furthermore, patients with antiphospholipid antibodies may experience alterations in coagulation, further contributing to an increased risk of infection [22].

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by the abnormal production of antiphospholipid antibodies, which elevates the risk of blood clot formation. The treatment for APS involves long-term oral anticoagulation therapy. However, during surgical procedures, patients with APS face a transiently increased risk of thromboembolism due to the temporary discontinuation of anticoagulants to achieve an international normalized ratio (INR) below 1.5 [22].

0.1.2.5 Metabolic conditions

Metabolic conditions such as hyperglycemia and poorly controlled diabetes mellitus, which are highly prevalent, could significantly influence the outcomes of any surgical procedure. These patients often experience post-operative tissue necrosis and have significantly longer hospital stays [24,25]. The increased incidence of wound infection in diabetes is primarily linked to hyperglycemia rather than the presence of diabetes itself. While individuals who have diabetes under control might not experience a greater risk of complications in relation to wound healing compared to those without diabetes. However, hyperglycemia exerts a negative impact on multiple elements of the wound healing process, encompassing immune system functionality like neutrophil and lymphocyte activity, chemotaxis, and phagocytosis. Moreover, increased levels of blood glucose impede the permeability of red blood cells and hinder blood flow in the essential small blood vessels surrounding the wound. This impediment subsequently disrupts the release of oxygen from hemoglobin, leading to inadequate oxygen supply and a deficiency of nutrients in the healing wound. Additionally, the occlusive disease of small blood vessels results in ischemia and limited cell recruitment, making the wound susceptible to bacterial and fungal infections [26].

Vitamin D is an indispensable nutrient for the human body as it plays a crucial role in regulating various physiological processes, including bone metabolism, immune system function, and the health of intestinal microbiota and barrier. In particular, a deficiency in Vitamin D has the potential to impede the proper healing of fractures, resulting in delayed healing and elevated susceptibility to post-traumatic bone loss. In addition to Vitamin D deficiency, both Crohn's disease and COPD have been extensively studied and demonstrated to exert substantial effects on bone metabolism [27,28].

Osteoporosis is identified by a decrease in bone mass and density, which increases the likelihood and occurrence of fractures. In the context of bone surgery, osteoporosis could have detrimental effects on the osteotomy sites, including delayed healing, poor split outcomes, and loosening of screws [29].

Obesity is defined as having a body weight that is 20% or more above the ideal weight. In obese patients, careful evaluation of their airway, cardiac function, and pulmonary status is necessary. Conversely, a low body mass index (BMI) should not be overlooked, particularly when there are signs of an eating disorder. In such cases, there might be nutritional deficiencies, significant cardiac changes, fluid and electrolyte imbalances, delayed gastric emptying, and severe endocrine abnormalities [30].

0.2. Orthognathic surgery

0.2.1 Brief introduction to orthognathic surgery

Orthognathic surgery is widely used to correct skeletal disharmonies of the jaw and face or other occlusion problems that cannot be treated with orthodontic treatment only. This surgery not only improves the appearance of patients, but also their oral function [31]. Orthognathic surgery has evolved significantly over the years in terms of techniques, technology, and patient care. The roots of orthognathic surgery can be traced back to the early 20th century when pioneers such as Vilray Blair introduced surgical techniques to correct facial deformities. In the 1950s and 1960s, William K. Harlan and others expanded the scope of orthognathic surgery and developed procedures to correct skeletal malocclusions [32]. Over time, surgical techniques for orthognathic surgery have become more refined and precise. Initially, procedures involved large incisions and extensive bone mobilization. However, the introduction of rigid internal fixation techniques utilizing plates and screws has provided surgeons with enhanced control over the repositioning of the jaw, resulting in more stable outcomes, reduced postoperative morbidity, and shorter hospital stays [33].

Presently, the primary surgical techniques employed in orthognathic surgery consist of Le Fort I osteotomy, bilateral sagittal split osteotomy, and osseous genioplasty. In the modern Le Fort I maxillary osteotomy, a surgical osteotomy is made from the nasal septum to the pterygomaxillary junction, below the apices of the maxillary teeth roots. This osteotomy enables the manipulation of maxilla in various directions, including anteroposterior, mediolateral, or superoinferior, allowing for the correction of deformities based on the functional and/or aesthetic requirements of the patient [34].

Sagittal split osteotomy (SSO), a mandibular osteotomy procedure, involves three main cuts. The procedure begins with the osteotomy of the cortical bone above the lingula on the inner side. This initial cut should extend past the mandibular foramen but does not necessarily need to reach the posterior border of the ramus entirely. Typically, it covers around half to two-thirds of the anteroposterior dimension of the ramus. The osteotomy then continues downward until it reaches the region of the first and second molars, following the external oblique ridge. It is crucial to keep the incision depth minimal, only enough to access the cancellous bone [35].

So far, significant progress has been made in orthognathic surgery in terms of techniques, planning, collaboration, and patient care. The use of advanced imaging technologies, such as cone-beam computed tomography (CBCT) systems and three-dimensional (3D) cephalometric analysis, has revolutionized the planning and execution of orthognathic surgery. These tools allow surgeons to assess the patient's skeletal structures accurately, plan surgical movements, and simulate the post-operative results [33]. Image-guided surgery is another trend that has gained popularity in recent years. This type of surgery enables the surgeon to track the location of the equipment and segments in real time while performing the procedure. Orthognathic surgery also makes use of modern intraoperative navigation systems [36]. The field continues to evolve with new technologies and techniques, making orthognathic surgery safer and more effective.

0.2.2 Brief introduction of complications following orthognathic surgery

While orthognathic surgery can bring about substantial improvement in both function and aesthetics, it is necessary to be aware of potential adverse outcomes that might arise during the recovery process, such as pain, swelling, hemorrhage, infection, respiratory complication, soft tissue damage, nerve injury, tooth damage, fracture/bad split, temporomandibular joint problems, relapse, bony necrosis, hearing problem, and change of nasal morphology. These complications might vary in severity and require additional treatment or management. In this introduction, the common complications that could arise following orthognathic surgery will be explored.

0.2.2.1 Infection

In healthy patients undergoing orthognathic surgery, the infection rate ranges from 3% to 21.6%, depending on a variety of risk factors connected to both the patient and the procedure [37–39]. Certain patient factors could impact the incidence of infection. For example, patients with compromised immune system, pre-existing oral infection, or systemic conditions such as diabetes may be at a higher risk. Smoking and poor oral hygiene also increase the likelihood of infection [40]. Surgical incisions in men and postmenopausal women could result in impaired collagen deposition and slower wound healing [41]. Additionally, age-related increase in thrombospondin 2, which inhibits angiogenesis, has been experimentally associated with delayed wound healing [42].

0.2.2.2 Nerve injury

The most typical complication encountered in patients who have undergone orthognathic surgery is neurosensory deficit, with reported rates ranging from 35% to 70% [43,44]. Inferior alveolar nerve, mental nerve, incisive nerve, and infraorbital nerve are most commonly affected by neurologic injuries that occur during orthognathic surgery [45]. After a peripheral nerve injury occurs, a cascade of intricate cellular and molecular signaling changes is triggered. The degree of functional recovery is closely associated with the molecular responses that strive to repair and restore the nerve to its state before the injury. Once inflammation and swelling subside in and around the nerve, sensory changes could be attributed to anatomical or functional modifications within the nerve itself or alterations induced in the central nervous system as a result of the nerve injury [46,47]. Le Fort I osteotomy could lead to sensory alterations in various areas, including the maxillary teeth, buccal mucosa, palatal mucosa, and facial skin. While skin sensation typically improves gradually over time, even after direct sensory nerve damage, it may not fully return to its pre-surgery condition [48]. Mandibular osteotomies performed near the neurovascular bundle within the mandibular canal pose a significant risk of damaging the inferior alveolar nerve. Electrophysiological indications of nerve injury could be detected at all stages of the osteotomy procedure [49]. The potential occurrence of nerve damage in orthognathic surgery might arise from the placement of semi-rigid fixation plates and screws. This deleterious outcome manifests either through direct nerve injury or as a consequence of nerve compression resulting from the fixation of screws between bony segments [50]. Neurological difficulties tend to be more common with sagittal split ramus osteotomy (SSRO) compared to intraoral vertical ramus osteotomy (IVRO) [51]. The incidence of sensory problems is also high with genioplasty [44].

0.2.2.3 Respiratory complication

In a previous study, respiratory difficulty was noted in 63 out of 301 patients who underwent orthognathic surgery, accounting for approximately 20.9% of the cases [44]. Complications associated with the respiratory system after orthognathic surgery include pneumomediastinum, pneumonia, airway obstruction, and pneumothorax [44]. Respiratory insufficiency following surgery could be influenced by several factors, including stimulation from anesthesia tubes, elevation or damage to the nasal mucous membrane, reduced nasal cavity space, intermaxillary fixation, potential blood aspiration, extended operation duration, and the influx of air through the neck fascial plane [52,53]. It is important to consider that the mandible's posterior movement during SSRO could significantly reduce the airway space. Predicting the risk of respiratory failure and determining the appropriate amount of mandibular setback could be beneficial in preventing potential postoperative issues. For patients classified as Class III malocclusion with high preoperative Mallampati scores, it is recommended to opt for minimal mandibular setback to mitigate potential respiratory complications [54]. In order to prevent dyspnea resulting from bleeding or accumulated secretions, avoiding excessive ventilation during general anesthesia and minimizing intraoperative trauma are crucial [55]. Respiratory difficulty necessitates immediate attention, with signs encompassing abnormal breathing, skin alterations, pain, and numbness. Prompt recognition and action are crucial to alleviate the problem and prevent further complications [44].

0.2.2.4 Bleeding / Hemorrhage

Orthognathic surgery typically results in some bleeding, with an average intraoperative volume of 436.11 mL [56]. Severe bleeding is an uncommon yet perilous complication, affecting 0.05-2.2% of cases [57,58]. The rich vascularity of the maxillofacial region and challenges associated with cauterization or ligation techniques contribute to the potential risk of substantial blood loss during surgical procedures in this area. The pterygoid plexus, palatal vessels, and internal maxillary artery are prone to bleeding during Le Fort I osteotomies, while the alveolar arteries and facial artery are involved in mandibular bleeding [56]. Proper surgical techniques, meticulous hemostasis, and monitoring are crucial to minimize the risk of extensive bleeding. Hypotensive anesthesia, positioning, and vasoconstrictor injections could help prevent bleeding [56]. In case of severe bleeding, interventions such as pressure application, hemostatic materials, or vessel ligation may be necessary. Increased intraoperative blood loss is associated with factors such as extensive surgical procedures, prolonged operating time, and low BMI. These factors contribute to a higher risk of significant blood loss during the surgical procedure [59]. In addition, hematomas are typically considered a minor issue, but their severity could escalate if they obstruct the airway or compress vital structures in sensitive areas. Hematomas are most commonly found on the floor of the mouth (0.58%), cheek (0.27%), submandibular area (0.18%), submental area (0.18%), and gingival channel (0.09%) [58].

0.2.2.5 Temporomandibular joint problems

Temporomandibular joint disorders (TMDs) encompass a range of clinical problems affecting the temporomandibular joint (TMJ), masticatory muscles, and the connective and soft tissue surrounding and adjacent to the TMJ, either individually or in combination. Common symptoms associated with TMDs include limited mandibular movement, pain in the masticatory muscles and TMJ, joint noises such as clicking, cracking, or crepitus, myofascial pain, and other functional limitations [60,61]. The correlation between craniofacial anomalies, malocclusion, and TMDs remains controversial. Some proponents suggest that mandibular setback surgery can effectively treat TMDs, while others argue that such surgery may exacerbate TMJ symptoms.

Le Fort I osteotomy is not typically associated with direct trauma to the TMJ or masticatory musculature, resulting in minimal effects on TMJ dysfunction or mandibular movement [62]. Regarding the outcomes of mandibular setback surgery using SSRO in relation to TMJ symptoms, different studies have reported varied results. Ueki et al. [63] discovered that 66.7% of patients experienced symptom relief following SSRO. However, Hu et al. [64] reported only a 40% improvement, with 8% of patients developing new TMJ issues. Kerstens et al. [65] noted a 66% improvement and an 11.5% worsening in TMJ symptoms, which contrasts with the findings of White and Dolwick [66], who reported an 89.1% improvement, 2.7 % stability, and 8.1 % worsening. Class III patients undergoing SSRO may experience slight posterior or lateral displacement of the condyle, but this does not have any noticeable impact on the location of the TMJ disc or the severity of postoperative discomfort [67]. Achieving precise reproduction of the original condylar position is challenging during bilateral sagittal split osteotomy (BSSO), and excessive pressure on the articular disc or unfavorable condylar positioning could occur during SSRO. These circumstances have the potential to lead to joint noise, pain, and exacerbation of pre-existing TMD symptoms [68–70]. Younger patients are particularly at risk of condylar alterations or resorption. The occurrence of pain and TMJ sounds during the initial months after surgery strongly indicate the possibility of condylar changes in the following months [71]. There is a predisposition for females to experience condylar resorption after SSO, potentially due to the influence of estrogen and prolactin [72]. Systemic diseases such as RA, scleroderma, SLE, and other vascular collagenous diseases are known as high-risk factors for condylar resorption [73]. High-angle patients have a larger tendency for horizontal skeletal relapse, primarily caused by condylar movement in the superior direction [74,75]. Changes in intercondylar angle and width resulting from sagittal split advancement or setback may impact TMJ function. Postoperative relapse of open bite resulting from condylar resorption typically occurs within a timeframe of 6 months to 3 years. Therefore, regular follow-up appointments are crucial early identification and intervention [76]. Pharmacotherapy options for managing this condition may include anti-inflammatory medications, tumor necrosis factor inhibitors, or matrix metalloproteinase inhibitors [77].

0.2.2.6. Relapse

Relapse, a commonly studied complication in orthognathic surgery, occurs at an incidence of approximately (5.3% to 33%) [78–80]. It is influenced by multiple factors, including physiological muscle effects, dentition position changes, condylar position during surgery, rotational movement of the distal segment, surgeon’s experience level, specific type of surgical intervention employed, sequential order of executed surgical procedures, and type of fixation employed. The occurrence of relapse could be attributed to various complications, including but not limited to bad splits, condylar displacement, and osteotomy slippage. Intrinsic factors, such as patient characteristics related to growth, BMI, occlusion, myofunction, and TMJ conditions, also play a significant role [81,82]. For Class III malocclusion, maxillary advancement procedures demonstrate higher stability with less relapse, while the degree of mandibular setback is positively associated with the extent of relapse [83]. In efforts to reduce the relapse rate, techniques such as posteriorly bending the distal segment in the mandibular, utilizing bone grafts for wider gaps, and considering plate fixation with bending have shown promising results [81,82].

0.3 State of the art on the relation between systemic diseases and orthognathic surgery

In order to gather evidence about postoperative complications following orthognathic surgery in patients with systemic diseases, a comprehensive literature search was conducted until April 2022. The inclusion criteria encompassed randomized controlled trials, prospective and retrospective studies, comparative, and non-comparative studies, as well as case series with a minimum of five patients. The results were limited to the English language. Screening of the articles yielded a total of 12,938 records, from which seven articles were deemed eligible and included in the analysis (Figure 1). The subsequent section presents the findings of the study.

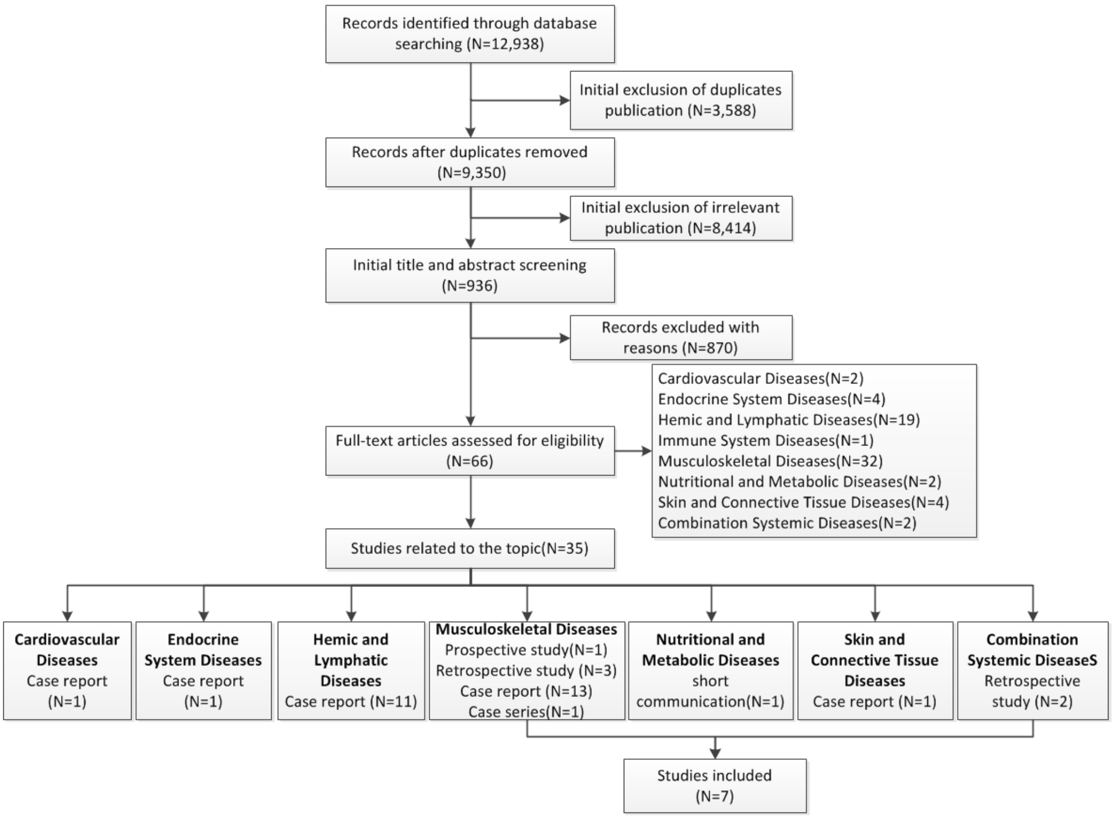


Figure 1. Flow chart of the literature search process.

0.3.1 Rheumatic diseases

Postoperative complications in patients with juvenile idiopathic arthritis (JIA), rheumatoid arthritis (RA), and spondyloarthropathy were reported [84–87]. Among the JIA patients, 25% of patients (12 patients) experienced skeletal relapse, defined as a horizontal displacement of pogonion in a posterior direction ⩾2 mm [84–86]. The average posterior relapse in these patients was 2.2 mm. Reoperation was required for eight patients (16%) at a time interval ranging from 2.4 months to 13.6 years after the initial surgery. Reasons for reoperation included relapse, persistent TMJ pain, and unsatisfactory postoperative outcomes [84,85]. The rate of postoperative relapse in patients with JIA fell within the range of relapse rate reported in a general orthognathic surgery population group (5.3% to 33%) [79,80]. However, the rate of reoperation was higher compared to the general population (0.2% to 2.4%), with the main reason being a residual retrognathic profile or open bite [37,43]. Although all of the patients underwent orthognathic surgery while JIA was in remission, none of the patients who received anti-rheumatic therapy during follow-up required reoperation, indicating that anti-rheumatic therapy might have a positive impact on postoperative skeletal stability [84]. In relation to anti-rheumatic therapy, intra-articular steroid injections have been suggested to be very effective for oligoarthritis [88]. Additionally, hydroxychloroquine and methotrexate, both of which are disease-modifying anti-rheumatic drugs (DMARD), have been recommended to be continued throughout the perioperative period for improving the orthognathic surgical outcome [89]. Since hydroxychloroquine is not an immunosuppressant, its safety profile is widely recognized. Several studies have also demonstrated the safety of methotrexate in the perioperative period for patients with RA and JIA; however, most of the evidence has been based on retrospective cohort studies [89,90].

Postoperative infection and abscess formation at the surgical site were observed in five patients (10%), who were treated with antibiotic therapy or incision and drainage [85,87]. The rate of postoperative infection (10%) was higher than the range of that observed in the general population (4% to 7.4%) [37,43,91,92]. Care should be taken in such cases as steroids offer a high risk of infection depending on the drug dosage and treatment duration [89,90,93]. As for the other commonly used perioperative medications administered to patients with rheumatic disorders, such as leflunomide and anti-TNF agents, conflicting data was observed related to their link with a higher risk of infection [90]. Thus, caution should be exercised until there is the availability of compelling evidence showing satisfactory wound healing [89].

In relation to the TMJ, three patients with JIA reported having persisting, new-onset, or even increased joint pain; however, no invasive intervention was required for the correction as it subsided at follow-up [85]. Based on the evidence, the majority of TMJ pain following orthognathic surgery could be managed with conservative therapy and anti-inflammatory medication, where only a minority might require arthroscopic surgery or reoperation. Also, female and older age patients have been associated with more functional problems and pain following surgery; however, no gender or age predilection was detected in the included studies [43,44].

0.3.2 Osteopenia and Osteoporosis

The study conducted by Yang et al. suggested a potential relationship between osteopenia and a backward clockwise skeletal relapse tendency of the mandible, with preoperative idiopathic condylar resorption as a possible confounding factor [94]. Some studies have shown that osteopenia and osteoporosis diminish bone density of cancellous bone and impair blood flow, which might cause osteomyelitis, slow healing, nonunion, screw loosening, and hardware failure [95,96]. Dental radiographs have been found to be highly effective in distinguishing osteoporosis/osteopenia from normal bone based on its density by measuring mandibular trabecular and inferior cortical thickness. The presence of sparse trabeculation in the premolar area, the existence of translucent lesions, or a cortical width of less than 3.0 - 4.5 mm in the mental foramen region are useful signs for detecting osteopenia or osteoporosis [97,98].

Lower serum Estradiol (E2) levels, as noted in patients with osteopenia, might cause cortical and medullary resorption in the condylar region by hindering the natural reparative capacity of the condyle in the presence of local inflammatory factors [94]. However, the relationship between low circulating E2 and skeletal relapse is uncertain and needs to be assessed [98]. All the aforementioned factors need to be considered, and the low bone density should be treated accordingly, thereby allowing surgeons to avoid the risk of relapse in such patients.

0.3.3 Myotonic dystrophy and congenital myopathy

In a study by Bezak et al. [99], six patients with neuromuscular disorders, including myotonic dystrophy and congenital myopathy, were investigated. All of these patients experienced postoperative respiratory complications, such as oxygen desaturation, heavy secretions, and acute respiratory arrest. Urgent bedside reintubation was necessary for four of these patients. The mean intubation time for all patients was 3.5 days (range: 0 to 6 days). The results indicated a higher risk of respiratory complications in patients with myotonic dystrophy and congenital myopathy [99]. The resulting weakness of respiratory musculature was directly associated with prolonged postoperative intubation or urgent reintubation. Patients with such disorders fail to properly clear bronchial secretions due to the inability to open small airways, leading to mucus impaction and oxygen desaturation. In a previous study, respiratory difficulty was observed in 63 out of 301 orthognathic surgery patients (20.9%) without any neuromuscular disorders, so its importance in patients with muscular disorders cannot be ignored [44]. Therefore, in patients where such a disorder is at hand, recognizing early signs or symptoms of respiratory distress is of utmost importance.

Additionally, the patients exhibited delayed recovery, possibly attributable to postoperative weakness in facial muscles, which could result in symptoms such as dysphagia, lower lip ptosis, and salivary drooling. When compounded with postsurgical edema, it could significantly delay the return to normal function [100]. Due to respiratory complications and delayed recovery, the mean length of hospital stay was seven days longer (mean: 10 days; range: 6 to 75 days) compared to that of the general population (mean: 3 days; range: 1.7 to 4.4 days) [43,101–104].

0.4 Aims and Hypotheses

Given the increasing prevalence of systemic diseases worldwide, it is of utmost importance to evaluate the postoperative outcomes of orthognathic surgery in patients with systemic diseases in order to enhance surgical outcomes and patient care. The primary objective of this Ph.D. thesis was to examine the impact of systemic diseases on postoperative outcomes in patients with orthognathic surgery. The secondary aim was to investigate the association between systemic diseases and postoperative complications, such as infection, bleeding, and impaired wound healing.

The research questions that guide this study were: What are the contributing factors to postoperative complications in orthognathic surgery patients with systemic diseases? How can we enhance postoperative outcomes in orthognathic surgery patients with systemic diseases? By addressing these research questions, this thesis aims to provide valuable insights into the management of orthognathic surgery patients with systemic diseases and offer recommendations for optimizing patient care.

This doctoral thesis is divided into two parts.

Part I: Prevalence of systemic diseases in orthognathic patients

Patients with systemic comorbidities present a unique risk profile that surgeons must be prepared to address, along with establishing preventive measures in advance. Surprisingly, there is a lack of available data on the prevalence and characteristics of underlying systemic diseases in the population of orthognathic surgery patients.

The objectives were:

- To assess the prevalence of systemic conditions in patients undergoing orthognathic surgery
- To investigate the demographic and clinical characteristics of systemic conditions in patients undergoing orthognathic surgery

The hypothesis was that:

A significant proportion of orthognathic patients have underlying systemic diseases, and certain systemic conditions may contribute to the development of malocclusion.

Part II: Complications in specific systemic diseases

A. Rheumatic diseases

When patients with rheumatic disorders undergo surgical treatment, they are at a greater risk of experiencing complications and adverse outcomes than those without these conditions. Most of the research related to surgical complications in patients with rheumatic disorders has generally focused on knee or hip joint replacement surgeries [105]. To the best of our knowledge, no study has particularly investigated the risk of complications in such patients following orthognathic surgery.

The objectives were:

- To provide a description of complications that may arise after orthognathic surgery in patients who suffer from rheumatic disorders.
- To determine whether or not rheumatic illness is a contributory factor in the development of these complications.

The hypothesis was that:

When compared to healthy individuals, those who suffer from rheumatic disorders have a greater likelihood of experiencing complications following orthognathic surgery.

B. Asthma

Asthma, a chronic respiratory condition characterized by airway inflammation and constriction, has emerged as a prominent comorbidity among patients with dentoskeletal deformities who are undergoing orthognathic surgery. Prior research indicates that asthmatic patients undergoing surgical procedures have a higher risk of complications after the operation than the general population [13].

The objective was:

- To evaluate the risk of postoperative problems following orthognathic surgery in asthmatic individuals in comparison to those who are in good overall condition.

The hypothesis was that:

Individuals who have asthma would show an increased susceptibility to complications after orthognathic surgery in contrast to non-asthmatic patients.

C. Autoimmune diseases

Autoimmune diseases encompass a range of disorders wherein the body's own antigens are erroneously identified as foreign, leading to the production of autoantibodies that attack native cells in tissues and organs. Due to the innate character of autoimmune diseases, the risk of complications following surgical procedures is elevated in patients with autoimmune disorders compared to those in good health.

The objective was:

- To explore the surgical results and problems that followed orthognathic surgery in patients who suffered from a variety of autoimmune disorders.

The hypothesis was that:

Patients who suffer from autoimmune disorders have a greater likelihood of experiencing postoperative complications following orthognathic surgery in comparison to people who are healthy.

0.5 References

[1] Ekmektzoglou KA, Zografos GC. A concomitant review of the effects of diabetes mellitus and hypothyroidism in wound healing. World J Gastroenterol 2006;12:2721–9. https://doi.org/10.3748/wjg.v12.i17.2721.

[2] Héla S, Nihel M, Faten L, Monia F, Jalel B, Azza F, et al. Osteoporosis and Crohn's disease. Jt Bone Spine 2005;72:403–7. https://doi.org/10.1016/j.jbspin.2004.09.006.

[3] Dobson R, Giovannoni G. Multiple sclerosis – a review. Eur J Neurol 2019;26:27–40. https://doi.org/https://doi.org/10.1111/ene.13819.

[4] Mayro RF, DeLozier IJB, Whitaker LA. Facial reconstruction consideration in rheumatic diseases. Rheum Dis Clin North Am 1991;17:943–69.

[5] Mathews JD, Whittingham S, Hooper BM, Mackay IR, Stenhouse NS. Association of autoantibodies with smoking, cardiovascular morbidity, and death in the Busselton population. Lancet 1973;302:754–8.

[6] Straub RH, Schradin C. Chronic inflammatory systemic diseases: An evolutionary trade-off between acutely beneficial but chronically harmful programs. Evol Med Public Heal 2016;2016:37–51. https://doi.org/10.1093/emph/eow001.

[7] Wilcox T, Smilowitz NR, Xia Y, Beckman JA, Berger JS. Cardiovascular Risk Factors and Perioperative Myocardial Infarction After Noncardiac Surgery. Can J Cardiol 2021;37:224–31. https://doi.org/10.1016/j.cjca.2020.04.034.

[8] Francula-Zaninovic S, Nola IA. Management of Measurable Variable Cardiovascular Disease Risk Factors. Curr Cardiol Rev 2018;14:153–63. https://doi.org/10.2174/1573403X14666180222102312.

[9] Adlesic EC. Cardiovascular Anesthetic Complications and Treatment in Oral Surgery. Oral Maxillofac Surg Clin North Am 2013;25:487-+. https://doi.org/10.1016/j.coms.2013.04.002.

[10] Marchac A, Arnaud E. Cranium and Midface Distraction Osteogenesis: Current Practices, Controversies, and Future Applications. J Craniofac Surg 2012;23:235–8. https://doi.org/10.1097/SCS.0b013e318241b96d.

[11] Nishiyama T, Hanaoka K. Does the common cold increase perioperative respiratory complications in adults? Masui 2005;54:643–7.

[12] Futran ND. Peterson's principles of oral and maxillofacial surgery, 2nd edition by Michael

Miloro, B.C. Decker, Inc., Hamilton, 2004. Head Neck 2006;28:378–9. https://doi.org/https://doi.org/10.1002/hed.20401.
[13] Lin C-S, Chang C-C, Yeh C-C, Chung C-L, Chen T-L, Liao C-C. Postoperative Adverse Outcomes in Patients With Asthma: A Nationwide Population-based Cohort Study. Medicine (Baltimore) 2016;95:e2548–e2548. https://doi.org/10.1097/MD.0000000000002548.
[14] Wood LG, Baines KJ, Fu J, Scott HA, Gibson PG. The Neutrophilic Inflammatory Phenotype Is Associated With Systemic Inflammation in Asthma. Chest 2012;142:86–93. https://doi.org/https://doi.org/10.1378/chest.11-1838.
[15] Hepner DL, Castells MC. Anaphylaxis during the perioperative period. Anesth Analg 2003;97:1381–95. https://doi.org/10.1213/01.ane.0000082993.84883.7d.
[16] Warner MA, Divertie MB, Tinker JH. Preoperative cessation of smoking and pulmonary complications in coronary artery bypass patients. Anesthesiology 1984;60:380–3. https://doi.org/10.1097/00000542-198404000-00022.
[17] Sin DD, Man SFP, Marciniuk DD, Ford G, FitzGerald M, Wong E, et al. Can inhaled fluticasone alone or in combination with salmeterol reduce systemic inflammation in chronic obstructive pulmonary disease? Study protocol for a randomized controlled trial. BMC Pulm Med 2006;6:3. https://doi.org/10.1186/1471-2466-6-3.
[18] Singh N. Systemic diseases of concern to prosthodontist. Int J Oral Heal Med Res 2015;2:89–93.
[19] Einy S, Ben-Barak A, Kridin K, Aizenbud D. Craniofacial Deformities in Patients With Beta-Thalassemia: Orthodontic Versus Surgical Correction-A Systematic Review. J Pediatr Hematol Oncol 2020;42:198–203. https://doi.org/10.1097/MPH.0000000000001651.
[20] Wong P, Fuller PJ, Gillespie MT, Milat F. Bone Disease in Thalassemia: A Molecular and Clinical Overview. Endocr Rev 2016;37:320–46. https://doi.org/10.1210/er.2015-1105.
[21] Rund D, Rachmilewitz E. Beta-thalassemia. N Engl J Med 2005;353:1135–46. https://doi.org/10.1056/NEJMra050436.
[22] Akkara Veetil BM, Bongartz T. Perioperative care for patients with rheumatic diseases. Nat Rev Rheumatol 2012;8:32–41. https://doi.org/10.1038/nrrheum.2011.171.
[23] Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population‐based study. Arthritis Rheum 2002;46:2287–93.
[24] Duggan EW, Carlson K, Umpierrez GE. Perioperative Hyperglycemia Management. Anesthesiology 2017;126:547–60. https://doi.org/10.1097/ALN.0000000000001515.
[25] Rahimi-Nedjat RK, Sagheb K, Pabst A, Foersch M, Jacobs C, Vollandt L, et al. Diabetes and hyperglycemia as risk factors for postoperative outcome in maxillofacial surgery. J Surg Res 2017;217:170–6. https://doi.org/10.1016/j.jss.2017.05.021.
[26] Goodson WH 3rd, Hunt TK. Wound healing and the diabetic patient. Surg Gynecol Obstet 1979;149:600–8.

[27] Syed N, Chiu GA, Korczak P. Should patients take vitamin D before mandibular operations? Br J Oral Maxillofac Surg 2017;55:841–3. https://doi.org/10.1016/j.bjoms.2017.07.004.

[28] Sertpoyraz FM, Deniz S. Bone mineral density and vitamin D levels in patients with group a COPD. Aging Male 2019:1–6. https://doi.org/10.1080/13685538.2019.1612869.

[29] On SW, Kim HJ, Kim J, Choi JW, Jung YW, Song SI. Effect of Osteoporosis on Bone Density of Orthognathic Osteotomy Sites in Maxillofacial Region. J Craniofac Surg 2016;27:e678–83. https://doi.org/10.1097/SCS.0000000000003064.

[30] Todd DW. Anesthetic considerations for the obese and morbidly obese oral and maxillofacial surgery patient. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 2005;63:1348–53. https://doi.org/10.1016/j.joms.2005.05.307.

[31] Naran S, Steinbacher DM, Taylor JA. Current Concepts in Orthognathic Surgery. Plast Reconstr Surg 2018;141:925e-936e. https://doi.org/10.1097/PRS.0000000000004438.

[32] Steinhauser EW. Historical development of orthognathic surgery. J Cranio-Maxillo-Facial Surg 1996;24:195–204.

[33] Dabir A, Vahanwala J. Orthognathic Surgery for the Maxilla-LeFort I and Anterior Maxillary Osteotomy BT - Oral and Maxillofacial Surgery for the Clinician. In: Bonanthaya K, Panneerselvam E, Manuel S, Kumar V V, Rai A, editors., Singapore: Springer Nature Singapore; 2021, p. 1513–48. https://doi.org/10.1007/978-981-15-1346-6_69.

[34] Buchanan EP, Hyman CH. LeFort I Osteotomy. Semin Plast Surg 2013;27:149–54. https://doi.org/10.1055/s-0033-1357112.

[35] Mani V. Orthognathic Surgery for Mandible BT - Oral and Maxillofacial Surgery for the Clinician. In: Bonanthaya K, Panneerselvam E, Manuel S, Kumar V V, Rai A, editors., Singapore: Springer Nature Singapore; 2021, p. 1477–512. https://doi.org/10.1007/978-981-15-1346-6_68.

[36] Constantinus Politis, Yi Sun, Tian Lei ES. Navigation in Orthognathic Surgery. Navig. Oral Maxillofac. Surg. Appl. Adv. Limitations, n.d., p. 51–60.

[37] Chow LK, Singh B, Chiu WK, Samman N. Prevalence of Postoperative Complications After Orthognathic Surgery: A 15-Year Review. J Oral Maxillofac Surg 2007;65:984–92. https://doi.org/10.1016/j.joms.2006.07.006.

[38] Bouchard C, Lalancette M. Infections after sagittal split osteotomy: a retrospective analysis of 336 patients. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 2015;73:158–61. https://doi.org/10.1016/j.joms.2014.07.032.

[39] Robl MT, Farrell BB, Tucker MR. Complications in Orthognathic Surgery: A Report of 1000 Cases. Oral Maxillofac Surg Clin North Am 2014;26:599–609. https://doi.org/https://doi.org/10.1016/j.coms.2014.08.008.

[40] Kuhlefelt M, Laine P, Suominen AL, Lindqvist C, Thorén H. Smoking as a Significant Risk Factor for Infections After Orthognathic Surgery. J Oral Maxillofac Surg 2012;70:1643–7. https://doi.org/https://doi.org/10.1016/j.joms.2011.06.224.

[41] Lenhardt R, Hopf HW, Marker E, Akça O, Kurz A, Scheuenstuhl H, et al. Perioperative collagen deposition in elderly and young men and women. Arch Surg 2000;135:71–4.
[42] Agah A, Kyriakides TR, Letrondo N, Björkblom B, Bornstein P. Thrombospondin 2 levels are increased in aged mice: consequences for cutaneous wound healing and angiogenesis. Matrix Biol 2004;22:539–47.
[43] Panula K, Finne K, Oikarinen K. Incidence of complications and problems related to orthognathic surgery: A review of 655 patients. J Oral Maxillofac Surg 2001;59:1128–36. https://doi.org/10.1053/joms.2001.26704.
[44] Kim SG, Park SS. Incidence of Complications and Problems Related to Orthognathic Surgery. J Oral Maxillofac Surg 2007;65:2438–44. https://doi.org/10.1016/j.joms.2007.05.030.
[45] Kim YK. Complications associated with orthognathic surgery. J Korean Assoc Oral Maxillofac Surg 2017;43:3–15. https://doi.org/10.5125/jkaoms.2017.43.1.3.
[46] Becerra L, Morris S, Bazes S, Gostic R, Sherman S, Gostic J, et al. Trigeminal neuropathic pain alters responses in CNS circuits to mechanical (brush) and thermal (cold and heat) stimuli. J Neurosci 2006;26:10646–57.
[47] Essick GK. Psychophysical assessment of patients with posttraumatic neuropathic trigeminal pain. J Orofac Pain 2004;18.
[48] Al-Din OF, Coghlan KM, Magennis P. Sensory nerve disturbance following Le Fort I osteotomy. Int J Oral Maxillofac Surg 1996;25:13–9. https://doi.org/10.1016/s0901-5027(96)80005-1.
[49] Panula K, Finne K, Oikarinen K. Neurosensory deficits after bilateral sagittal split ramus osteotomy of the mandible—influence of soft tissue handling medial to the ascending ramus. Int J Oral Maxillofac Surg 2004;33:543–8.
[50] Nakagawa K, Ueki K, Takatsuka S, Takazakura D, Yamamoto E. Somatosensory-evoked potential to evaluate the trigeminal nerve after sagittal split osteotomy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91:146–52. https://doi.org/10.1067/moe.2001.112331.
[51] Hasegawa T, Tateishi C, Asai M, Imai Y, Okamoto N, Shioyasono A, et al. Retrospective study of changes in the sensitivity of the oral mucosa: Sagittal split ramus osteotomy (SSRO) versus intraoral vertical ramus osteotomy (IVRO). Int J Oral Maxillofac Surg 2015;44:349–55. https://doi.org/10.1016/j.ijom.2014.10.016.
[52] Virkkula P, Hurmerinta K, Löytönen M, Salmi T, Malmberg H, Maasilta P. Postural cephalometric analysis and nasal resistance in sleep-disordered breathing. Laryngoscope 2003;113:1166–74. https://doi.org/10.1097/00005537-200307000-00012.
[53] Kim T, Kim JY, Woo YC, Park SG, Baek CW KH. Pneumomediastinum and pneumothorax after orthognathic surgery: A case report. Maxillofac Plast Reconstr Surg 2010;32:246–50. https://doi.org/10.4097/kjae.2010.59.S.S242.
[54] Choi S-K, Yoon J-E, Cho J-W, Kim J-W, Kim S-J, Kim M-R. Changes of the Airway Space and the Position of Hyoid Bone after Mandibular Set Back Surgery Using Bilateral Sagittal Split Ramus Osteotomy Technique. Maxillofac Plast Reconstr Surg 2014;36:185–91.

https://doi.org/10.14402/jkamprs.2014.36.5.185.
[55] Kim Y-K. Complications associated with orthognathic surgery. J Korean Assoc Oral Maxillofac Surg 2017;43:3.
[56] Piñeiro-Aguilar A, Somoza-Martín M, Gandara-Rey JM, García-García A. Blood loss in orthognathic surgery: a systematic review. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 2011;69:885–92. https://doi.org/10.1016/j.joms.2010.07.019.
[57] Sousa CS, Turrini RNT. Complications in orthognathic surgery: A comprehensive review. J Oral Maxillofac Surgery, Med Pathol 2012;24:67–74. https://doi.org/https://doi.org/10.1016/j.ajoms.2012.01.014.
[58] Acebal-Bianco F, Vuylsteke PLPJ, Mommaerts MY, De Clercq CAS. Perioperative complications in corrective facial orthopedic surgery: a 5-year retrospective study. J Oral Maxillofac Surg 2000;58:754–60.
[59] Thastum M, Andersen K, Rude K, Nørholt SE, Blomlöf J. Factors influencing intraoperative blood loss in orthognathic surgery. Int J Oral Maxillofac Surg 2016;45:1070–3. https://doi.org/10.1016/j.ijom.2016.02.006.
[60] Wadhwa S, Kapila S. TMJ disorders: future innovations in diagnostics and therapeutics. J Dent Educ 2008;72:930–47.
[61] Jung H-D, Kim SY, Park H-S, Jung Y-S. Orthognathic surgery and temporomandibular joint symptoms. Maxillofac Plast Reconstr Surg 2015;37:14. https://doi.org/10.1186/s40902-015-0014-4.
[62] Boyd SB, Karas ND, Sinn DP. Recovery of mandibular mobility following orthognathic surgery. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 1991;49:924–31. https://doi.org/10.1016/0278-2391(91)90054-p.
[63] Ueki K, Marukawa K, Nakagawa K, Yamamoto E. Condylar and temporomandibular joint disc positions after mandibular osteotomy for prognathism. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 2002;60:1424. https://doi.org/10.1053/joms.2002.36098.
[64] Hu J, Wang D, Zou S. Effects of mandibular setback on the temporomandibular joint: a comparison of oblique and sagittal split ramus osteotomy. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 2000;58:371–5. https://doi.org/10.1016/s0278-2391(00)90915-7.
[65] Kerstens HC, Tuinzing DB, van der Kwast WA. Temporomandibular joint symptoms in orthognathic surgery. J Cranio-Maxillo-Facial Surg Off Publ Eur Assoc Cranio-Maxillo-Facial Surg 1989;17:215–8. https://doi.org/10.1016/s1010-5182(89)80071-x.
[66] White CS, Dolwick MF. Prevalence and variance of temporomandibular dysfunction in orthognathic surgery patients. Int J Adult Orthodon Orthognath Surg 1992;7:7–14.
[67] Farella M, Michelotti A, Bocchino T, Cimino R, Laino A, Steenks MH. Effects of orthognathic surgery for Class III malocclusion on signs and symptoms of temporomandibular disorders and on pressure pain thresholds of the jaw muscles. Int J Oral Maxillofac Surg 2007;36:583–7. https://doi.org/10.1016/j.ijom.2007.02.001.

[68] Hackney FL, Van Sickels JE, Nummikoski P V. Condylar displacement and temporomandibular joint dysfunction following bilateral sagittal split osteotomy and rigid fixation. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 1989;47:223–7. https://doi.org/10.1016/0278-2391(89)90221-8.

[69] Ellis E 3rd, Hinton RJ. Histologic examination of the temporomandibular joint after mandibular advancement with and without rigid fixation: an experimental investigation in adult Macaca mulatta. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 1991;49:1316–27. https://doi.org/10.1016/0278-2391(91)90311-9.

[70] Buckley MJ, Tulloch JF, White RPJ, Tucker MR. Complications of orthognathic surgery: a comparison between wire fixation and rigid internal fixation. Int J Adult Orthodon Orthognath Surg 1989;4:69–74.

[71] Borstlap WA, Stoelinga PJW, Hoppenreijs TJM, van't Hof MA. Stabilisation of sagittal split advancement osteotomies with miniplates: a prospective, multicentre study with two-year follow-up. Part III--condylar remodelling and resorption. Int J Oral Maxillofac Surg 2004;33:649–55. https://doi.org/10.1016/j.ijom.2004.01.018.

[72] Arnett GW, Milam SB, Gottesman L. Progressive mandibular retrusion—idiopathic condylar resorption. Part I. Am J Orthod Dentofac Orthop 1996;110:8–15.

[73] Huang YL, Pogrel MA, Kaban LB. Diagnosis and management of condylar resorption. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 1997;55:114–20. https://doi.org/10.1016/s0278-2391(97)90222-6.

[74] Merkx MA, Van Damme PA. Condylar resorption after orthognathic surgery. Evaluation of treatment in 8 patients. J Cranio-Maxillo-Facial Surg Off Publ Eur Assoc Cranio-Maxillo-Facial Surg 1994;22:53–8. https://doi.org/10.1016/s1010-5182(05)80297-5.

[75] Hwang SJ, Haers PE, Zimmermann A, Oechslin C, Seifert B, Sailer HF. Surgical risk factors for condylar resorption after orthognathic surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;89:542–52. https://doi.org/10.1067/moe.2000.105239.

[76] Hoppenreijs TJ, Stoelinga PJ, Grace KL, Robben CM. Long-term evaluation of patients with progressive condylar resorption following orthognathic surgery. Int J Oral Maxillofac Surg 1999;28:411–8.

[77] Gunson MJ, Arnett GW, Milam SB. Pathophysiology and pharmacologic control of osseous mandibular condylar resorption. J Oral Maxillofac Surg 2012;70:1918–34. https://doi.org/10.1016/j.joms.2011.07.018.

[78] Bharti D, Mohindru DK, Shetty DV, Khanna DSS, Gowdar DIM, Tiwari DRVC, et al. Evaluation Of Relapse In Orthognathic Surgery: An Original Research. Eur J Mol Clin Med 2020;7:3210–5.

[79] Proffit WR, Turvey TA, Phillips C. The hierarchy of stability and predictability in orthognathic surgery with rigid fixation: An update and extension. Head Face Med 2007;3:1–11. https://doi.org/10.1186/1746-160X-3-21.

[80] Catherine Z, Breton P, Bouletreau P. Condylar resorption after orthognathic surgery: A systematic review. Rev Stomatol Chir Maxillofac Chir Orale 2016;117:3–10. https://doi.org/10.1016/j.revsto.2015.11.002.

[81] Lee J-H, Lee I-W, Seo B-M. Clinical analysis of early reoperation cases after orthognathic surgery. Jkaoms 2010;36:28–38. https://doi.org/10.5125/jkaoms.2010.36.1.28.

[82] Van Sickels JE, Dolce C, Keeling S, Tiner BD, Clark GM, Rugh JD. Technical factors accounting for stability of a bilateral sagittal split osteotomy advancement Wire osteosynthesis versus rigid fixation. Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology 2000;89:19–23. https://doi.org/https://doi.org/10.1016/S1079-2104(00)80008-6.

[83] de Haan IF, Ciesielski R, Nitsche T, Koos B. Evaluation of relapse after orthodontic therapy combined with orthognathic surgery in the treatment of skeletal class III. J Orofac Orthop 2013;74:362–9. https://doi.org/10.1007/s00056-013-0161-0.

[84] Stoor P, Hodzic Z, Arte S. Surgical Treatment of Dentofacial Deformities Caused by Juvenile Idiopathic Arthritis. J Craniofac Surg 2018;29:e51–7. https://doi.org/10.1097/SCS.0000000000004029.

[85] Oye F, Bjornland T, Store G. Mandibular osteotomies in patients with juvenile rheumatoid arthritic disease. Scand J Rheumatol 2003;32:168–73. https://doi.org/10.1080/03009740310002515.

[86] Leshem D, Tompson B, Britto JA, Forrest CR, Phillips JH. Orthognathic surgery in juvenile rheumatoid arthritis patients. Plast Reconstr Surg 2006;117:1941–6. https://doi.org/10.1097/01.prs.0000209922.46292.58.

[87] Brijs K, Peeters H, Politis C. Orthognathic surgery in patients with systemic diseases. Oral Maxillofac Surg 2022. https://doi.org/10.1007/s10006-022-01054-1.

[88] Hashkes PJ, Laxer RM. Medical Treatment of Juvenile Idiopathic Arthritis. JAMA 2005;294:1671–84. https://doi.org/10.1001/jama.294.13.1671.

[89] Goodman SM, Figgie M. Lower extremity arthroplasty in patients with inflammatory arthritis: preoperative and perioperative management. J Am Acad Orthop Surg 2013;21:355–63. https://doi.org/10.5435/JAAOS-21-06-355.

[90] Krause ML, Matteson EL. Perioperative management of the patient with rheumatoid arthritis. World J Orthop 2014;5:283–91. https://doi.org/10.5312/wjo.v5.i3.283.

[91] Jedrzejewski M, Smektala T, Sporniak-Tutak K, Olszewski R. Preoperative, intraoperative, and postoperative complications in orthognathic surgery: a systematic review. Clin Oral Investig 2015;19:969–77. https://doi.org/10.1007/s00784-015-1452-1.

[92] Choi SH, Lee SJ, Jung YS, Shin YS, Jun DB, Hwang KH, et al. Nitroglycerin- and Nicardipine-Induced Hypotension Does Not Affect Cerebral Oxygen Saturation and Postoperative Cognitive Function in Patients Undergoing Orthognathic Surgery. J Oral Maxillofac Surg 2008;66:2104–9. https://doi.org/10.1016/j.joms.2008.06.041.

[93] Kasapçopur Ö, Barut K. Treatment in juvenile rheumatoid arthritis and new treatment options.

Turk Pediatr Ars 2015;50:1–10. https://doi.org/10.5152/tpa.2015.2229.

[94] Yang HJ, Hwang SJ. Bone mineral density and mandibular advancement as contributing factors for postoperative relapse after orthognathic surgery in patients with preoperative idiopathic condylar resorption: A prospective study with preliminary 1-year follow-up. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;120:112–8. https://doi.org/10.1016/j.oooo.2015.03.004.

[95] Carlson BC, Robinson WA, Wanderman NR, Sebastian AS, Nassr A, Freedman BA, et al. A Review and Clinical Perspective of the Impact of Osteoporosis on the Spine. Geriatr Orthop Surg Rehabil 2019;10:215145931986159. https://doi.org/10.1177/2151459319861591.

[96] Bjerke BT, Zarrabian M, Aleem IS, Fogelson JL, Currier BL, Freedman BA, et al. Incidence of Osteoporosis-Related Complications Following Posterior Lumbar Fusion. Glob Spine J 2018;8:563–9. https://doi.org/10.1177/2192568217743727.

[97] Jonasson G, Bankvall G, Kiliaridis S. Estimation of skeletal bone mineral density by means of the trabecular pattern of the alveolar bone, its interdental thickness, and the bone mass of the mandible. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:346–52. https://doi.org/10.1067/moe.2001.116494.

[98] Karayianni K, Horner K, Mitsea A, Berkas L, Mastoris M, Jacobs R, et al. Accuracy in osteoporosis diagnosis of a combination of mandibular cortical width measurement on dental panoramic radiographs and a clinical risk index (OSIRIS): The OSTEODENT project. Bone 2007;40:223–9. https://doi.org/10.1016/j.bone.2006.07.025.

[99] Bezak BJ, Arce KA, Jacob A, Van Ess J. Orthognathic Surgery in Patients with Congenital Myopathies and Congenital Muscular Dystrophies: Case Series and Review of the Literature. J Oral Maxillofac Surg 2016;74:601–9. https://doi.org/10.1016/j.joms.2015.07.023.

[100] Manzon S, Philbert R. Orthognathic Surgery in a Patient With Myotonic Dystrophy: Review of Literature and Report of a Case. J Oral Maxillofac Surg 2007;65:2575–9. https://doi.org/10.1016/j.joms.2006.03.047.

[101] Jarab F, Omar E, Bhayat A, Mansuri S, Ahmed S. Duration of Hospital Stay Following Orthognathic Surgery at the Jordan University Hospital. J Maxillofac Oral Surg 2012;11:314–8. https://doi.org/10.1007/s12663-011-0327-5.

[102] Moles DR, Cunningham SJ. A national review of mandibular orthognathic surgery activity in the National Health Service in England over a nine year period. Part 1 - Service factors. Br J Oral Maxillofac Surg 2009;47:268–73. https://doi.org/10.1016/j.bjoms.2008.10.020.

[103] Huaman ET, Juvet LM, Nastri A, Denman WT, Kaban LB, Dodson TB, et al. Changing patterns of hospital length of stay after orthognathic surgery. J Oral Maxillofac Surg 2008;66:492–7. https://doi.org/10.1016/j.joms.2007.08.025.

[104] Van Strijen PJ, Breuning KH, Becking AG, Perdijk FBT, Tuinzing DB. Cost, operation and hospitalization times in distraction osteogenesis versus sagittal split osteotomy. J Cranio-Maxillofacial Surg 2003;31:42–5. https://doi.org/10.1016/S1010-5182(02)00161-0.

[105] Bongartz T, Halligan CS, Osmon DR, Reinalda MS, Bamlet WR, Crowson CS, et al. Incidence and risk factors of prosthetic joint infection after total hip or knee replacement in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2008;59:1713–20. https://doi.org/https://doi.org/10.1002/art.24060.

Part I

Prevalence of systemic diseases in orthognathic patients

Article 1

Prevalence and characteristics of systemic conditions in patients undergoing orthognathic surgery: a retrospective study

Jonas Ver Berne [1]

Jiqing Li [1]

Eman Shaheen [1]

Constantinus Politis [1]

Hilde Peeters [2]

Reinhilde Jacobs [1,3]

[1] OMFS IMPATH research group, Department of Imaging & Pathology, Faculty of Medicine, KU Leuven and Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium

[2] Center for Human Genetics, University Hospitals Leuven, Leuven, Belgium

[3] Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden

Published in:

International Journal of Oral and Maxillofacial Surgery. 2022; 51: 1205–1210

1.1 Abstract

The aim of this study was to investigate the prevalence and characteristics of systemic conditions in patients undergoing orthognathic surgery at a tertiary center. Ninety of the 838 patients undergoing orthognathic surgery between 2013 and 2019 had a systemic condition (prevalence of 10.7%). The most prevalent categories of systemic conditions were inflammatory joint disorders, endocrinological disorders, and syndromes. Patients with syndromes were significantly younger at the time of surgery than patients with endocrinological ($P < 0.001$), inflammatory joints ($P = 0.003$), or gastrointestinal disorders ($P = 0.033$). Endocrinological disorders, syndromes, and malignancies were more frequently associated with a skeletal Class III malocclusion ($P = 0.009$, $P < 0.001$, and $P = 0.048$ respectively). Further research is needed to clarify the role of systemic conditions in the aetiology of malocclusion and postoperative outcomes.

Keywords: endocrinology; orthognathic surgery; prevalence; postoperative complications; malocclusion.

1.2 Introduction

The impact of several systemic conditions on the maxillofacial skeleton has been well established. In patients with haemophilia and diabetes mellitus, decreased bone mineralization, delayed wound healing, and impaired fracture healing have been observed [1–3]. Diseases like juvenile idiopathic arthritis (JIA) and Crohn's disease have also been associated with decreased bone mineral density, both because of systemic inflammation and the chronic use of corticosteroids [4,5]. Besides the higher risk of infectious complications in these patients, decreased bone mineral density has been hypothesized to contribute to the occurrence of bad splits and postoperative relapse [6,7]. In 1988, Moyers defined six etiological categories of malocclusion: hereditary, developmental cause of unknown origin, trauma, physical agents, habits, and diseases [8]. However, the role of systemic comorbidities was not well understood.

Since then, rheumatic and endocrinological disorders have been implicated in the development of malocclusion. Rheumatic diseases cause inflammation of the synovial membranes in the joints, which leads to the destruction of cartilage and bone [9]. In the maxillofacial region, this is the classic presentation of JIA, resulting in a Class II malocclusion [10]. Acromegaly due to growth hormone excess causes mandibular prognathism and a Class III malocclusion, often starting in adulthood [11].

It appears that there are no available data on the prevalence and characteristics of patients with underlying systemic conditions in an orthognathic surgery population. Furthermore, diseases other than JIA have been poorly studied regarding associated types of malocclusions. Therefore, this study aimed to assess the prevalence of systemic conditions in patients undergoing orthognathic surgery. As a secondary objective, the demographic and clinical characteristics of these patients were investigated.

1.3 Materials and Methods

A retrospective analysis was conducted to determine the prevalence and characteristics of systemic conditions in an orthognathic surgery population. The study patients were treated in the Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Belgium (a tertiary center) between April 2013 and May 2019. Patient records relevant to the research question were identified and the extracted data were structured for analysis. The patients were then classified into a study group (systemic conditions) and a healthy group (no systemic conditions). Within the study group, patients were classified into relevant categories. Ethical approval was obtained from the Ethics Committee for Research of the University Hospitals/Catholic University Leuven (S64994).

Patients with an active systemic condition or a history of a systemic condition who underwent orthognathic surgery were included. 'Systemic condition' was defined as a medical condition affecting multiple organs or tissues, or affecting the body as a whole [12]. Patients receiving chemotherapy for a systemic or non-systemic malignancy were also included, as were patients with syndromes. Syndromes were defined as a conglomerate of anatomical/morphological manifestations that frequently occur together. When a clear dominance of one particular feature was present, these patients were reclassified into the appropriate category of systemic conditions. Orthognathic surgery was defined as any or a combination of the following procedures to correct a skeletal malocclusion: bilateral sagittal split osteotomy, Le Fort I, II, or III osteotomies, Schuchardt osteotomy, Sandwich osteotomy, Wunderer osteotomy, and genioplasty. Patients were classified by their primary systemic disease (i.e., the disease with the most profound systemic effect).

The data were analyzed using JASP version 0.14 statistical software (Department of Psychological Methods, University of Amsterdam, Nieuwe Achtergracht 129B, Amsterdam, The Netherlands). A 6-year prevalence was calculated at the patient level. Characteristics of the two study groups were compared using the Pearson X^2 test and the unpaired t-test. In addition, logistic regression analysis was performed to compare the relationship between age and sex in the study groups. The Pearson X^2 test was used to evaluate differences in sex and malocclusion between different categories and the healthy group. When test assumptions were not met, Fisher's exact test was used. The Kruskal–Wallis *H*-test was used to compare age at the time of surgery between the different categories of systemic conditions. The results are presented as the mean standard deviation (SD) for normally distributed variables or as the median and interquartile range (IQR) for non-normally distributed variables. The significance level was set at $P < 0.05$.

1.4 Results

1.4.1 Comparison between the systemic conditions group and the healthy group

A total of 838 patients who underwent orthognathic surgery between April 2013 and May 2019 were identified from the medical records (Figure 1). Among these patients, 90 (10.7%) had a systemic condition. A comparison of demographic characteristics between patients with and without systemic conditions is presented in Table 1. Additional logistic regression analysis between the two groups showed a difference in the relationship between age and sex (Figure 2). In the healthy group, there was an equal distribution of male and female patients across the age range (odds ratio 0.99, P = 0.404), whereas in the study group, older patients were mostly female (odds ratio 0.95, P = 0.009).

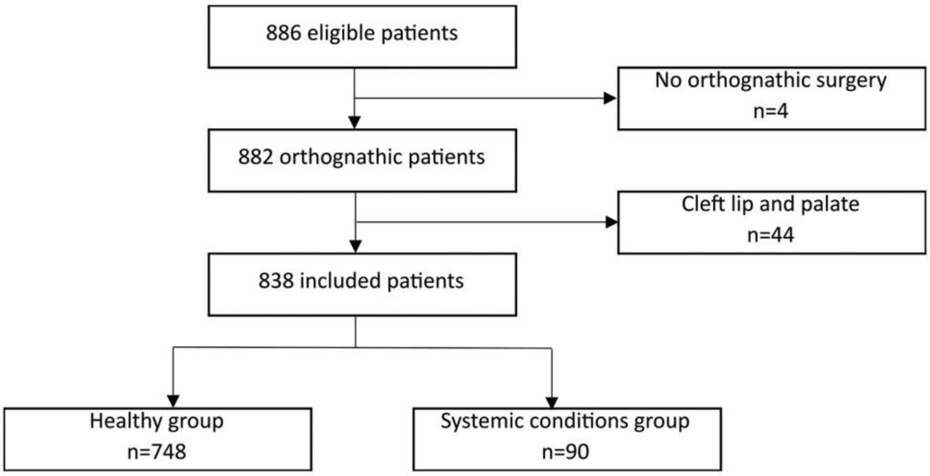


Figure 1. Flowchart of the patient selection process.

Table 1. Comparison of clinical and demographic characteristics between the healthy group (no systemic conditions) and the study group (systemic conditions).

	Healthy group (*n* = 748)	Study group (*n* = 90)	*P*-value
Age (years), mean ± SD	26.10 ± 11.60	30.34 ± 14.53	0.0042[a]*
Sex, *n* (%)			0.1102[b]
Female	459 (61.4)	63 (70)	
Male	289 (38.6)	27 (30)	
Malocclusion, *n* (%)			<0.001[b]*
Class II	527 (70.5)	48 (53.3)	
Class III	221 (29.5)	42 (46.7)	

SD, standard deviation.

[a] Unpaired Welch *t*-test. [b] Pearson X^2 test. *$P < 0.05$, significant result.

1.4.2 Comparison of demographic characteristics between categories of systemic conditions

Patients in the study group were classified into 10 categories of systemic conditions. The number of patients and demographic characteristics per category are reported in Table 2. No significant sex differences were found between the categories ($P = 0.110$). The Kruskal–Wallis *H*-test showed a significant difference in age at the time of surgery between the categories of systemic conditions ($H(9) = 31.165$, $P < 0.001$). Post hoc comparison located these differences between syndromes and endocrinological ($P < 0.001$), gastrointestinal ($P = 0.033$), and inflammatory joint disorders ($P = 0.003$) (Figure 3).

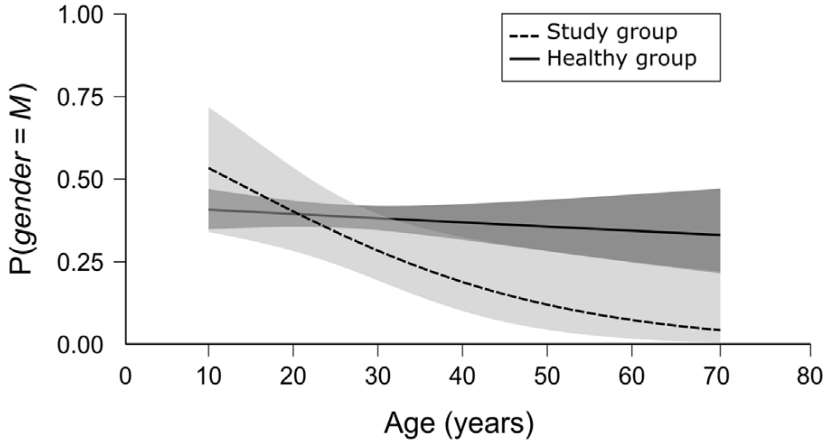


Figure 2. Logistic regression analysis of the relationship between sex and age in the healthy group and study group. The graph shows the probability with a 95% confidence interval of being male across the age range. No significant relationship was observed in the healthy group (odds ratio 0.99, *P* = 0.404). In the study group, older patients were less likely to be male (odds ratio 0.95, *P* = 0.009).

Table 2. Patient sex and age distribution according to the categories of systemic conditions in the study group.

Classification	Patients (*n*)	Sex		Age (years), median (IQR)
		Female	Male	
Inflammatory joint disorders	17	14	3	31.0 (26.0)
Metabolic bone disorders	2	2	0	38.5 (20.5)
Endocrinological disorders	17	14	3	38.0 (19.0)
Connective tissue disorders	7	6	1	24.0 (16.0
Syndromes	20	10	10	17.0 (4.0)
Hematological disorders	4	2	2	47.0 (12.3)
Gastrointestinal disorders	6	5	1	42.0 (8.8)
Malignancies	6	2	4	18.5 (3.0)
Neurological disorders	2	2	0	37.5 (11.5)
Miscellaneous	9	6	3	24.0 (4.0)
Total	90	63	27	25.0 (25.0)

IQR, interquartile range.

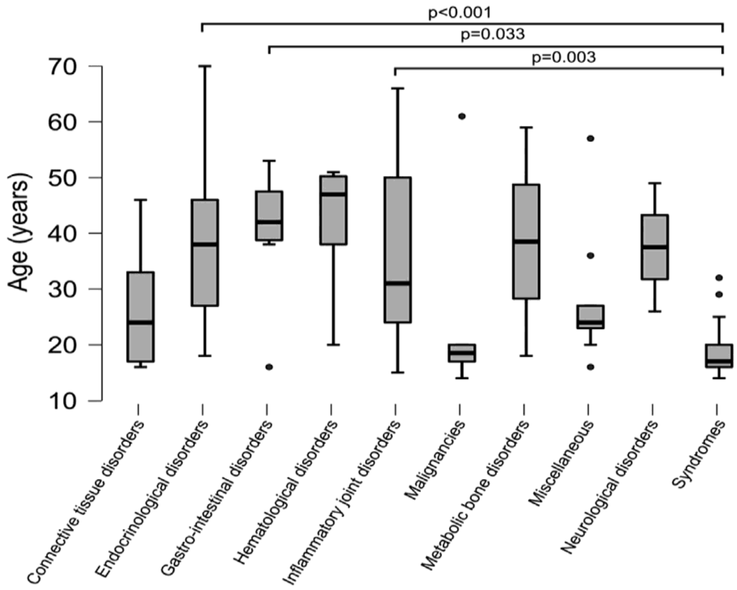


Figure 3. Boxplot of the age distribution within each category of systemic conditions. The Kruskal–Wallis *H*-test showed significant differences in age at the time of surgery between syndromes and endocrinological, gastrointestinal, and inflammatory joint disorders (*P*-values displayed).

1.4.3 Comparison of clinical characteristics according to the categories of systemic conditions

The distribution of skeletal malocclusion per category of systemic condition and per systemic condition is displayed in Supplementary Material Table S1. The Pearson X^2 test and Fisher's exact test showed significant associations between a class III malocclusion and endocrinological disorders ($P = 0.009$), syndromes ($P < 0.001$), and malignancies ($P = 0.048$). In the study group, three patients had major adverse outcomes postoperatively that required re-intervention. The clinical information of these cases is presented in Table 3.

Table 3. Clinical characteristics of patients in the study group with adverse outcomes.

Case	Dentofacial diagnosis	Surgical procedure	Systemic condition	Adverse outcome	Treatment
1	Class III	Le Fort I osteotomy with midline split	Fibromyalgia	Backwards relapse of the maxilla	Intermaxillary fixation with class III elastic traction
2	Class III	SARPE – Hyrax Bimax with genioplasty	Neurofibromatosis type 1	Non-union maxilla, backwards relapse of the right mandible	Bone graft maxilla, BSSO advancement right mandible
3	Class II	Bimax (three-piece maxilla) with genioplasty	Henoch–Schoenlein vasculitis	Left midline shift maxilla, broadened nasal base	Genioplasty, redo alar cinch

Bimax, bimaxillary osteotomy; BSSO, bilateral sagittal split osteotomy; SARPE, surgically-assisted rapid palatal expansion.

1.5 Discussion

This retrospective study showed that approximately one in 10 patients undergoing orthognathic surgery had a systemic condition. The most prevalent categories of systemic conditions were inflammatory joint disorders, endocrinological disorders, and syndromes. However, compared to the results of the National Health Survey of 2018 in Belgium, inflammatory joint diseases were much less common in the study orthognathic population (2%) than in the general population (7%) [13]. Other chronic conditions less common in the present study were diabetes mellitus (0.6% vs. 5.9%), thyroid diseases (1% vs. 7%), and osteoporosis (0.1% vs. 3.3%). As the majority of these diseases present after adolescence, a lower prevalence in an orthognathic population is expected. Also, the self-reporting nature of the National Health Survey may have resulted in an overestimation of the actual prevalence of several chronic conditions in the general population. When compared to the literature, some specific conditions were more prevalent in the present study population than in the general population, e.g., JIA (0.8% vs 0.007–0.40%) [14], Ehlers–Danlos syndrome (0.6% vs 0.02 - 0.2%) [15,16], inflammatory bowel diseases (0.5% vs 0.0.5%) [17], neurofibromatosis type 1 (0.5% vs 0.017 - 0.033%) [18], and Marfan syndrome (0.2% vs 0.02 - 0.03%) [19].

The results of this study showed a difference in age at the time of surgery between patients with syndromes and patients with endocrinological, gastrointestinal, and inflammatory joint disorders. Patients with syndromes requiring surgery to correct a skeletal malocclusion are often operated on at a young age, in multiple phases, and with a variety of surgical techniques (distraction osteogenesis or orthognathic surgery). Any (residual) malocclusion is corrected as soon as possible after maturation of the facial skeleton. Furthermore, maxillary hypoplasia could be surgically corrected at an earlier age than mandibular hyperplasia, explaining the younger age in this category of patients. In contrast, a mixed proportion of midface hypoplasia and mandibular hyperplasia was observed in patients with endocrinological disorders, implicating an older average age at surgery. Due to the need to control joint inflammation prior to surgery, patients with inflammatory joint disorders are also operated on at a later age.

Associations were observed between syndromes and a Class III malocclusion, and between malignancies and a Class III malocclusion. Craniofacial syndromes are often the result of genetic mutations causing halted or aberrant growth of the facial skeleton, leading to a Class II or III malocclusion [20]. Although the differential development of patients to a Class II or III malocclusion is highly syndrome-specific, many genetic pathways are implicated in the craniofacial development in these patients. This makes it impossible to draw general conclusions from this varied patient pool.

Deformities in patients with malignancies are the result of tumor location in the maxillofacial region, local radiotherapy to the midface, or systemic chemotherapy, all leading to distortion or growth restriction of the affected skeleton. On the other hand, the results of this study also showed an association between endocrinological disorders and a Cass III malocclusion, without an obvious cause. Fundamental research has linked the fibroblast growth factor (FGF) pathway, regulated by thyroid hormones, to changes in bone metabolism [21]. Gain-of-function mutations in the FGF3 gene have been observed in patients with Muenke syndrome and achondroplasia with a Class III malocclusion [22], while loss-of-function mutations in the FGF1 and FGF2 genes have been associated with a Class II malocclusion [23,24]. However, mechanisms linking systemic conditions and malocclusion are unlikely to be this simple, and a combination of multiple functional and genetic driving forces needs to be considered in the development of any type of malocclusion [25].

Adverse outcomes were reported in three patients in the study group. In patients with neurofibromatosis type 1, the NF1-encoded protein neurofibromin contains a GAP-related domain that activates Ras-GTPase [26]. This regulates the development of craniofacial structures and leads to bone demineralization, increasing the risk of postoperative relapse [6,27,28]. In addition to genetic factors, malocclusion and relapse could be a result of tumor invasion and local destruction [29]. This same pattern of bone demineralization has been shown in patients with fibromyalgia [30]. Also in patients with vasculitis, decreased bone mineralization could occur due to systemic inflammation or chronic use of corticosteroids [31]. However, most of the evidence implicating systemic conditions in bone demineralization is indirect or of low quality, and no direct association with surgical outcomes has been investigated.

The absence of certain systemic conditions in the study group merits an explanation. Several patients with muscle dystrophy in wheelchairs, as well as syndromic patients with extremely restricted lung capacity, were deemed unfit for orthognathic surgery. In addition, a number of patients were not included due to the fact that they received other treatments beyond the reach of orthognathic surgery. Even though the envelope of discrepancies that could be corrected with orthognathic surgery exceeds the orthodontic potential, in some syndromic instances, discrepancies of more than 2 standard deviations from the normal need reconstructive procedures (e.g., costochondral grafts, craniofacial procedures, and alloplastic joint procedures).

Due to the retrospective nature of this study, some biases and limitations should be considered. First, only the sample of patients undergoing orthognathic surgery was assessed to report on deviating values for patients with systemic conditions. The comparative results should be projected onto a global group of patients not surgically corrected for their skeletal malocclusion. It is therefore assumed that the reported study population only contains the patients with the most severe degrees of malocclusion. Moreover, being a tertiary center, University Hospitals Leuven attracts both elective patients and referrals for specific medical problems. This may also have contributed to the high prevalence of systemic conditions seen in the current study. Lastly, although a large sample of 90 patients with systemic conditions was obtained, many categories contained only a few patients with a specific systemic condition. Generalized conclusions in these groups of patients may thus be of limited value.

1.6 Conclusion

This study is novel in reporting on patients with systemic conditions undergoing orthognathic surgery. Due to the large sample size, it was possible to obtain significant results and give an initial overview of this patient population. Further large-sample studies are needed to confirm the results, explore the etiological mechanisms of skeletal malocclusion more deeply, and investigate the complication rate in this specific population.

1.7 References

[1] Camargo WA, de Vries R, van Luijk J, Hoekstra JW, Bronkhorst EM, Jansen JA, et al. Diabetes Mellitus and Bone Regeneration: A Systematic Review and Meta-Analysis of Animal Studies. Tissue Eng Part B Rev 2016;23:471–9. https://doi.org/10.1089/ten.teb.2016.0370.

[2] Marin C, Luyten FP, Van der Schueren B, Kerckhofs G, Vandamme K. The Impact of Type 2 Diabetes on Bone Fracture Healing. Front Endocrinol (Lausanne) 2018;9:6. https://doi.org/10.3389/fendo.2018.00006.

[3] Anagnostis P, Karras S, Paschou SA, Goulis DG. Haemophilia A and B as a cause for secondary osteoporosis and increased fracture risk. Blood Coagul Fibrinolysis an Int J Haemost Thromb 2015;26:599–603. https://doi.org/10.1097/MBC.0000000000000330.

[4] Burnham JM, Shults J, Dubner SE, Sembhi H, Zemel BS, Leonard MB. Bone density, structure, and strength in juvenile idiopathic arthritis: Importance of disease severity and muscle deficits. Arthritis Rheum 2008;58:2518–27. https://doi.org/10.1002/art.23683.

[5] Sgambato D, Gimigliano F, De Musis C, Moretti A, Toro G, Ferrante E, et al. Bone alterations in inflammatory bowel diseases. World J Clin Cases 2019;7:1908–25. https://doi.org/10.12998/wjcc.v7.i15.1908.

[6] Yang HJ, Hwang SJ. Bone mineral density and mandibular advancement as contributing factors for postoperative relapse after orthognathic surgery in patients with preoperative idiopathic condylar resorption: A prospective study with preliminary 1-year follow-up. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;120:112–8.

https://doi.org/10.1016/j.oooo.2015.03.004.
[7] On SW, Kim HJ, Kim J, Choi JW, Jung YW, Song SI. Effect of Osteoporosis on Bone Density of Orthognathic Osteotomy Sites in Maxillofacial Region. J Craniofac Surg 2016;27:e678–83. https://doi.org/10.1097/SCS.0000000000003064.
[8] Moyers RE. Handbook of orthodontics. 4th edition. Year Book Medical Publishers; n.d. https://doi.org/LK - https://worldcat.org/title/1023896437.
[9] Mellins ED, MacAubas C, Grom AA. Pathogenesis of systemic juvenile idiopathic arthritis: Some answers, more questions. Nat Rev Rheumatol 2011;7:416–26. https://doi.org/10.1038/nrrheum.2011.68.
[10] Hu Y, Billiau AD, Verdonck A, Wouters C, Carels C. Variation in dentofacial morphology and occlusion in juvenile idiopathic arthritis subjects: A case-control study. Eur J Orthod 2009;31:51–8. https://doi.org/10.1093/ejo/cjn085.
[11] Vilar L, Vilar CF, Lyra R, Lyra R, Naves LA. Acromegaly: clinical features at diagnosis. Pituitary 2017;20:22–32. https://doi.org/10.1007/s11102-016-0772-8.
[12] Wan D. Dorland's illustrated medical dictionary. 28th edition. Saunders; 2010. Consulted online at www.dorlandsonline. com on august 17, 2020.
[13] Van Der Heyden J CR. Chronische ziekten en aandoeningen. Brussels, Belgium: Sciensano (Belgisch instituut voor gezondheid); 2018.
[14] Barut K, Adrovic A, Şahin S, Kasapçopur Ö. Juvenile idiopathic arthritis. Balkan Med J 2017;34:90–101. https://doi.org/10.4274/balkanmedj.2017.0111.
[15] Wilcox WR. Connective Tissue and Its Heritable Disorders: Molecular, Genetic, and Medical Aspects. Am J Hum Genet 2003;72:503.
[16] Demmler JC, Atkinson MD, Reinhold EJ, Choy E, Lyons RA, Brophy ST. Diagnosed prevalence of Ehlers-Danlos syndrome and hypermobility spectrum disorder in Wales, UK: a national electronic cohort study and case-control comparison. BMJ Open 2019;9:31365. https://doi.org/10.1136/bmjopen-2019-031365.
[17] Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2017;390:2769–78. https://doi.org/10.1016/S0140-6736(17)32448-0.
[18] Bergqvist C, Servy A, Valeyrie-Allanore L, Ferkal S, Combemale P, Wolkenstein P, et al. Neurofibromatosis 1 French national guidelines based on an extensive literature review since 1966. Orphanet J Rare Dis 2020;15. https://doi.org/10.1186/s13023-020-1310-3.
[19] Ramirez F, Dietz HC. Marfan syndrome: from molecular pathogenesis to clinical treatment. Curr Opin Genet Dev 2007;17:252–8. https://doi.org/10.1016/j.gde.2007.04.006.
[20] Bartzela TN, Carels C, Maltha JC. Update on 13 syndromes affecting craniofacial and dental structures. Front Physiol 2017;8:1038. https://doi.org/10.3389/fphys.2017.01038.
[21] Leitch VD, Bassett JHD, Williams GR. Role of thyroid hormones in craniofacial development.

Nat Rev Endocrinol 2020;16:147–64. https://doi.org/10.1038/s41574-019-0304-5.

[22] Lee YC, Song IW, Pai YJ, Chen S De, Chen YT. Knock-in human FGFR3 achondroplasia mutation as a mouse model for human skeletal dysplasia. Sci Rep 2017;7. https://doi.org/10.1038/srep43220.

[23] Merrill AE, Sarukhanov A, Krejci P, Idoni B, Camacho N, Estrada KD, et al. Bent bone dysplasia-FGFR2 type, a distinct skeletal disorder, has deficient canonical FGF signaling. Am J Hum Genet 2012;90:550–7. https://doi.org/10.1016/j.ajhg.2012.02.005.

[24] Jarzabek K, Wolczynski S, Lesniewicz R, Plessis G, Kottler M.L. Evidence that FGFR1 loss-of-function mutations may cause variable skeletal malformations in patients with Kallmann syndrome. Adv Med Sci 2012;57:314–21. https://doi.org/10.2478/v10039-012-0036-4.

[25] Da Fontoura CSG, Miller SF, Wehby GL, Amendt BA, Holton NE, Southard TE, et al. Candidate gene analyses of skeletal variation in malocclusion. J Dent Res 2015;94:913–20. https://doi.org/10.1177/0022034515581643.

[26] Bergoug M, Doudeau M, Godin F, Mosrin C, Vallée B, Bénédetti H. cells Neurofibromin Structure, Functions and Regulation. https://doi.org/10.3390/cells9112365.

[27] Wang W, Nyman JS, Ono K, Stevenson DA, Yang X, Elefteriou F. Mice lacking Nf1 in osteochondroprogenitor cells display skeletal dysplasia similar to patients with neurofibromatosis type I. Hum Mol Genet 2011;20:3910–24. https://doi.org/10.1093/hmg/ddr310.

[28] Sharma R, Wu X, Rhodes SD, Chen S, He Y, Yuan J, et al. Hyperactive Ras/MAPK signaling is critical for tibial nonunion fracture in neurobromin-decient mice. Hum Mol Genet 2013;22:4818–28. https://doi.org/10.1093/hmg/ddt333.

[29] Alwan S, Armstrong L, Joe H, Birch PH, Szudek J, Friedman JM. Associations of osseous abnormalities in neurofibromatosis. Am J Med Genet Part A 2007;143:1326–33. https://doi.org/10.1002/ajmg.a.31754.

[30] Upala S, Yong WC, Sanguankeo A. Bone mineral density is decreased in fibromyalgia syndrome: a systematic review and meta-analysis. Rheumatol Int 2017;37:617–22. https://doi.org/10.1007/s00296-016-3625-x.

[31] Kirnap M, Calis M, Kaya N, Muhtaroglu S. Is the Behcet's disease a risk factor for osteoporosis and is relation to cytokines? Bratisl Lek Listy 2010;111:340–4.

Article 2

Prevalence of systemic conditions in an orthognathic surgery population: A 20-year single-center study

Jonas Ver Berne [1,2]

Constantinus Politis [1,2]

Joeri Meyns [1,3]

Jiqing Li [1,2]

Reinhilde Jacobs [1,2,4]

[1] OMFS-IMPATH Research Group, Department of Imaging and Pathology, Group Biomedical Sciences, Catholic University Leuven, Leuven, Belgium

[2] Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium.

[3] Department of Oral and Maxillofacial Surgery, Ziekenhuis Oost- Limburg, Genk, Belgium

[4] Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden

Published in:

Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology. 2022 Aug;134(2):163-167.

2.1 Abstract

Objective: To describe the prevalence and characteristics of patients with systemic conditions in an orthognathic surgery population.

Study Design: A retrospective review was conducted of 1653 patients undergoing orthognathic surgery between 2001 and 2020. Patients were grouped per category of systemic condition and relevant information was retrieved from medical records. Clinical and perioperative characteristics were compared between patients with and without systemic conditions using x^2 tests and 95% confidence intervals. Age was compared using a cumulative logit model.

Results: The proportion of patients with systemic conditions undergoing orthognathic surgery was 16% (272 of 1653 patients). Patients with systemic conditions were on average 6 years older than patients without systemic conditions ($P < .001$). Significant differences in age compared to healthy patients were found for endocrinological (12 years; 95% confidence interval (CI), 8-16 years), gastrointestinal (10 years; 95% CI, 3-18 years), pneumological (5 years; 95% CI, 2-13 years), and cardiovascular disorders (17 years; 95% CI, 12-21 years).

Conclusion: Nearly 1 out of 6 patients undergoing orthognathic surgery has a systemic condition. Knowledge of the prevalence and characteristics of these patients creates awareness among surgeons and a foundation for future studies on perioperative management.

2.2 Introduction

Orthognathic surgery is considered a routine therapy for patients with malocclusions and facial deformities. Different osteotomies (e.g., bilateral sagittal split osteotomy, Le Fort I, or segmental osteotomies) are frequently combined to achieve the desired outcome. Currently, the presence of systemic conditions mainly has implications for the anesthesiologist rather than for the maxillofacial surgeon. However, certain comorbidities may require special consideration in the planning, treatment, or follow-up of these patients.

There are many studies investigating the effect of systemic conditions on bone metabolism and general wound healing. For example, patients with diabetes mellitus are known to be more susceptible to postoperative infections than the general population [1]. In addition, they experience qualitative bone changes, with loss of strength, increased fracture risk, and impaired bone healing as a result (both type 1 and type 2 diabetes mellitus) [2,3]. Patients with bleeding disorders (e.g., hemophilia A/B and Von Willebrand's disease) require specialized pre-, peri-, and postoperative management because they are predisposed to developing extensive hematomas [4]. In addition, hemophilia A and B are increasingly associated with decreased bone mineral density, which in turn has been linked to impaired fracture healing [5,6]. Hypothyroidism results in impaired collagen synthesis, which also results in delayed or defective wound healing of soft tissues as well as bone [7].

However, little research exists about these systemic conditions in the context of orthognathic surgery. In this article, we aim to investigate the prevalence of systemic conditions in an orthognathic surgery population. The sub-objective is to assess any differences in clinical and perioperative characteristics between these patients and the healthy orthognathic population.

2.3 Materials and Methods

Medical records of all consecutive patients undergoing orthognathic surgery at Ziekenhuis Oost-Limburg in Genk, Belgium, between 2001 and 2020 were reviewed. Orthognathic surgery was defined as mandibular (e.g., bilateral sagittal split) and/or maxillary (e.g., Le Fort) osteotomy to correct a skeletal malocclusion, with or without genioplasty. Only patients with a clearly defined malocclusion diagnosis and recorded type of surgery were included. Because medical records made no distinction between sporadic and syndromic cleft lip and palate, these patients were excluded. A total of 1653 patients were included for analysis (Figure 1). Ethics approval was obtained from the Clinical Trial Unit and Ethics Committee of the Ziekenhuis Oost-Limburg hospital (internal reference number 19/0088R).

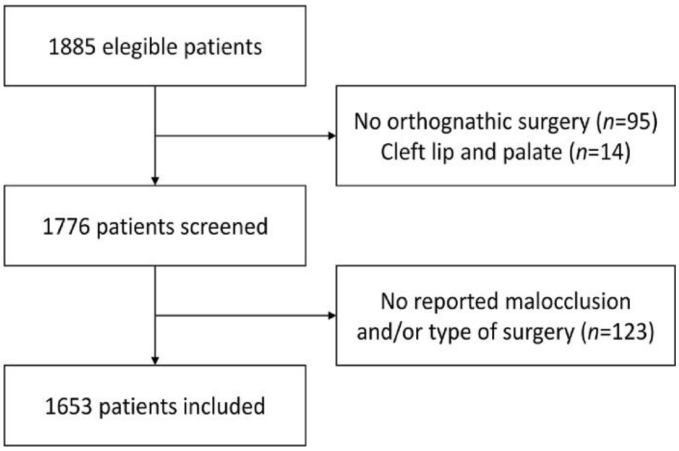


Figure 1. Flowchart of the patient screening and inclusion process.

To describe the prevalence and characteristics of patients with systemic conditions, we grouped patients according to the presence or absence of systemic conditions. Next, a total of 13 categories of systemic conditions were created as per organ system involved. For each patient, we collected sex, age at the time of surgery (years), length (centimeters), weight (kilograms), skeletal malocclusion diagnosis (Angle classification), type of surgery, duration of surgery (minutes), and blood loss during surgery (milliliters).

Data are summarized as mean and SD for normally distributed, median and interquartile range for nonnormally distributed, and absolute counts and percentages for categorical data. First, the patient groups with and without systemic conditions were compared for all variables collected. For normal distributed and categorical data, the z-interval was used to compare the means and proportions respectively. Due to nonnormality, blood loss, duration of surgery, and age at the time of surgery were categorized and evaluated using a cumulative logit model. Second, malocclusion diagnoses and age at the time of surgery were compared between the categories of systemic conditions. Proportions of malocclusion diagnosis were evaluated using the x^2 test. Fisher's exact test was used when cells with expected values < 5 were encountered. Using Bonferroni's correction for multiple testing, we set the significance level at $p = a/k = 0.004$ for $k = 13$ comparisons. Because of small sample sizes and nonnormality of the data, age at the time of surgery was evaluated by creating confidence intervals around medians using bootstrapping with 1000 samples. Data were analyzed by a licensed statistician using R v.4.1.0.

2.4 Results

2.4.1 Prevalence of systemic conditions

In our orthognathic surgery population, the prevalence of patients with systemic conditions was 16% (272 of 1653 patients). Among these patients, a total of 341 systemic conditions were distributed (Table I). The most prevalent categories of systemic disorders were neurological (61 patients, 18%), cardiovascular (54 patients, 16%), pneumological (51 patients, 16%), gastrointestinal (34 patients, 10%), and endocrinological (34 patients, 9%)

2.4.2 Differences between patients with and without systemic conditions

Compared to patients without systemic conditions, patients with systemic conditions were a median of 3 kg heavier (95% confidence interval, 1-5 kg). No differences were observed for types of surgeries between the 2 groups (Table II). Using a cumulative logit model, we found that patients with systemic conditions underwent surgery at a later age than patients without systemic conditions (Table III). These results are statistically significant at all thresholds ($P < 0.001$).

Table I. Demographic and clinical characteristics of the total study population

Variable	Total sample, n (%)
Total number	1653 (100)
Sex	
Male	614 (37)
Female	1039 (63)
Malocclusion diagnosis	
Class II malocclusion	1194 (72)
Class III malocclusion	459 (28)
Patients with systemic conditions	272 (17)
Distribution of systemic conditions	341 (-)
Inflammatory joint disorders	9 (3)
Endocrinological disorders	35 (9)
Connective tissue disorders	2 (1)
Syndromic conditions	12 (4)
Hematological disorders	14 (4)
Gastrointestinal disorders	35 (10)
Malignancies	3 (1)
Neurological disorders	61 (18)
Pneumological disorders	51 (16)
Nephrological disorders	7 (2)
Cardiovascular disorders	54 (16)
Miscellaneous	55 (16)

2.4.3 Differences between categories of systemic conditions

No differences in malocclusion diagnoses between categories of systemic conditions could be demonstrated. When comparing different categories to the patient group without systemic conditions, median age at the time of surgery was higher in patients with endocrinological, gastrointestinal, pneumological, and cardiovascular disorders (Table IV). Patients with connective tissue disorders had a median age of 32 years higher than the group without systemic conditions. However, due to the small sample size of only 2 patients, these results cannot be extrapolated to the total population. Similarly, patients with miscellaneous conditions had a median age of 4 years higher, but the heterogeneous nature of this category leaves this result without meaning.

Table II. Comparison of demographic and clinical variables between patient groups with and without systemic conditions

Variable	No systemic condition group (n = 1381)	Systemic condition group (n = 272)	Difference	95% CI
Sex, *n* (%)				
Male	522 (38)	92 (34)	4	-2 to 10
Female	859 (62)	180 (66)	-4	-10 to 2
Malocclusion diagnosis, *n* (%)				
Class II	987 (71)	207 (76)	-5	-10 to 1
Class III	394 (29)	65 (24)	5	-1 to 10
Type of surgery, *n* (%)				
BSSO	704 (51)	137 (51)	0	-7 to 7
Le Fort 1	111 (8)	21 (8)	0	-4 to 4
Bimaxillary surgery	561 (41)	111 (41)	0	-6 to 6
Genioplasty	249 (18)	50 (18)	0	-5 to 5
SARPE	139 (10)	32 (12)	-2	-6 to 2
Normally distributed variables				
Height, mean, cm (SD)	171.0 (9.5)	170.2 (8.9)	0.8	-0.4 to 2.0
Weight, mean, kg (SD)	64.0 (13.3)	67.0 (17.1)	3.0*	1.0 to 5.0

Categorical data are displayed as proportions with differences in absolute percentage points and confidence intervals calculated using the z-interval for normally distributed approximations. Normal data are displayed as means with differences and confidence intervals calculated using the z-test for normal distributions.
CI, confidence interval; *BSSO*, bilateral sagittal split osteotomy. *SARPE*, surgically assisted rapid palatal expansion.
*Significant.

Table III. Cumulative logit model for differences in age at the time of surgery, perioperative blood loss, and duration of surgery between patient groups with and without systemic conditions

Threshold	% Under threshold no systemic conditions	% Under threshold systemic conditions	Odds ratio	95% CI
Age at the time of surgery				
20 y	44.5	29.3	1.93*	1.45 - 2.58
30 y	70.0	54.8	1.92*	1.46 - 2.52
40 y	86.6	74.5	2.21*	1.6 - 3.05
50 y	96.7	90.7	2.96*	1.77 - 4.97
Perioperative blood loss				
50 mL	0.5	2.0	0.23	0.04 - 1.28
100 mL	50.9	52.5	0.94	0.62 - 1.42
150 mL	55.7	53.5	1.09	0.72 - 1.66
200 mL	64.5	60.4	1.19	0.78 - 1.82
250 mL	71.7	68.3	1.18	0.75 - 1.84
300 mL	75.9	69.3	1.40	0.89 - 2.2
350 mL	93.1	93.1	1.01	0.45 - 2.28
Duration of surgery				
60 min	2.0	1.9	1.07	0.24 - 4.67
90 min	5.0	1.9	2.68	0.64 - 11.27
120 min	51.2	50.5	1.03	0.69 - 1.55
150 min	62.0	60.0	1.09	0.72 - 1.65
180 min	70.2	70.5	0.98	0.63 - 1.54
210 min	86.4	85.7	1.06	0.59 - 1.89

Groups were compared using a cumulative logit model with threshold limits as depicted in the table.
CI, confidence interval.
* Significant.

Table IV. Differences in malocclusion diagnosis and age at the time of surgery between categories of systemic conditions

	Malocclusion			Age at surgery (years)		
Systemic condition	Class II (%)	Class III (%)	P value	Median (IQR)	Difference	95% CI
No systemic conditions group (*n* = 1381)	73	27	—	21 (17-32)	—	—
Inflammatory joint disorders (*n* = 9)	78	22	0.684	27 (20-36)	6	-28 to 2
Endocrinological disorders (*n* = 35)	83	17	0.117	33 (24-44)	12*	8 to16
Connective tissue disorders (*n* = 2)	50	50	0.496	53 (48-58)	32*	23 to 41
Syndromic conditions (*n* = 12)	75	25	0.798	18 (16-21)	3	-6 to2
Hematological disorders (*n* = 14)	79	21	0.566	25.5 (18-48)	5	-4 to 26
Gastrointestinal disorders (*n* = 35)	66	34	0.428	31 (22-41)	10*	3 to 18
Malignancies (*n* = 3)	0	100	0.006	51 (32-52)	30	-9 to 31
Neurological disorders (*n* = 61)	79	21	0.216	19 (17-29)	2	-3 to2
Pneumological disorders (*n* = 51)	75	25	0.649	26 (21-41)	5*	2 to13
Nephrological disorders (*n* = 7)	71	29	0.988	28 (23-34)	7	4 to 17
Cardiovascular disorders (*n* = 54)	73	27	0.796	37.5 (27-48)	17*	12 to 21
Miscellaneous (*n* = 55)	78	22	0.277	26 (20-38)	5*	2 to 9

Malocclusion distribution was compared to the patient group without systemic conditions using Pearson's chi-square and Fisher's exact tests. No significant differences were observed. Age at the time of surgery for each category was compared to the group without systemic conditions. Confidence intervals were calculated with bootstrapping using 1000 samples. IQR, interquartile range; CI, confidence interval.
*Significant.

2.5 Discussion

This 2-decade retrospective study shows that almost 1 in 6 patients undergoing orthognathic surgery has a systemic condition that is relevant to the oral and maxillofacial surgeon. The most prevalent conditions in our study—asthma, hypertension, attention deficit and hyperactivity disorder (ADHD), and hypothyroidism—are important to consider both pre- and post-operatively. In a retrospective study on 10,345 patients undergoing orthognathic surgery, Venugoplan et al. found the most common comorbidities to be chronic pulmonary disease (8.3% of all hospitalizations), arterial hypertension (7.2%), depression (3.6%), obesity (3.2%), deficiency anemias (2.5%), and hypothyroidism (2.1%) [8]. However, no correlation was made between comorbidities and other patient characteristics such as type of malocclusion or complication rate. The high prevalence of these chronic conditions may correlate with the higher age (mean, 26.7 years) of the patients compared to our study.

The most significant differences between the groups with and without systemic conditions were age at the time of surgery and weight. The effect of age and weight on recovery after surgery has been well established. Both weight and BMI are significant risk factors for wound infection, increased perioperative blood loss, and longer operating times [9]. Also, patients with obesity frequently have multiple cardiovascular comorbidities, which may increase the surgical risk. These factors combined with the systemic condition itself may alter the postoperative outcome in these patients. Further research on complications in this population is necessary to evaluate the relative importance of each of these factors.

When comparing malocclusion diagnosis between the categories of systemic diseases and the total study sample, no associations could be demonstrated. However, when looking at the excluded patients with cleft lip and palate, a clear association with a Class III malocclusion was observed (92% Class III). This observation has an obvious cause and has been well-established in both clinical practice and the literature [10,11]. Other systemic conditions (e.g., juvenile idiopathic arthritis) have been associated with Class II skeletal malocclusion in the past [12]. However, these results could not be replicated in our study despite the large study sample. Given that we only investigated patients undergoing orthognathic surgery, several patients with mild skeletal malocclusions not needing surgery may have been overlooked. Children with juvenile idiopathic arthritis who received orthodontic activator therapy for a Class II malocclusion are also not included in our population, further underestimating the proportion of skeletal malocclusion in these patients. These factors strongly impair the generalizability of the results to patients not undergoing orthognathic surgery.

2.6 Conclusion

Patients with systemic conditions are well-represented in the total orthognathic surgery population. Many of these conditions require the attention of oral and maxillofacial surgery before, during, and after surgery. Higher relapse rates and respiratory difficulties are some of the most frequent complications that occur in these patients [13,14]. Perioperative medical management should therefore be tailored to the individual patient in order to minimize the medical as well as surgical complication risk. Reporting the prevalence of these conditions, this article creates awareness among surgeons regarding the high prevalence of these conditions. Further research is needed to assess the outcomes after orthognathic surgery in patients with systemic conditions.

2.7 References

[1] Raikundalia M, Svider PF, Hanba C, Folbe AJ, Shkoukani MA, Baredes S, et al. Facial fracture repair and diabetes mellitus: An examination of postoperative complications. Laryngoscope 2017;127:809–14. https://doi.org/https://doi.org/10.1002/lary.26270.

[2] Camargo WA, de Vries R, van Luijk J, Hoekstra JW, Bronkhorst EM, Jansen JA, et al. Diabetes Mellitus and Bone Regeneration: A Systematic Review and Meta-Analysis of Animal Studies. Tissue Eng Part B Rev 2016;23:471–9. https://doi.org/10.1089/ten.teb.2016.0370.

[3] Marin C, Luyten FP, Van der Schueren B, Kerckhofs G, Vandamme K. The Impact of Type 2 Diabetes on Bone Fracture Healing. Front Endocrinol (Lausanne) 2018;9:6. https://doi.org/10.3389/fendo.2018.00006.

[4] Holtzman LS, Burns ER, Kraut RA. Preoperative laboratory assessment of hemostasis for orthognathic surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1992;73:403–6. https://doi.org/10.1016/0030-4220(92)90314-g.

[5] Anagnostis P, Karras S, Paschou SA, Goulis DG. Haemophilia A and B as a cause for secondary osteoporosis and increased fracture risk. Blood Coagul Fibrinolysis an Int J Haemost Thromb 2015;26:599–603. https://doi.org/10.1097/MBC.0000000000000330.

[6] Hak DJ. The biology of fracture healing in osteoporosis and in the presence of anti-osteoporotic drugs. Injury 2018;49:1461–5. https://doi.org/10.1016/j.injury.2018.04.016.

[7] Ekmektzoglou KA, Zografos GC. A concomitant review of the effects of diabetes mellitus and hypothyroidism in wound healing. World J Gastroenterol 2006;12:2721–9. https://doi.org/10.3748/wjg.v12.i17.2721.

[8] Venugoplan SR, Nanda V, Turkistani K, Desai S, Allareddy V. Discharge patterns of orthognathic surgeries in the United States. J Oral Maxillofac Surg 2012;70:e77–86. https://doi.org/10.1016/j.joms.2011.09.030.

[9] Tjeertes EKM, Hoeks SE, Beks SBJ, Valentijn TM, Hoofwijk AGM, Stolker RJ. Obesity--a risk factor for postoperative complications in general surgery? BMC Anesthesiol 2015;15:112. https://doi.org/10.1186/s12871-015-0096-7.

[10] Téllez-Conti C, Mora-Diaz II, Díaz-Báez D, Ocampo-Arias IJ, Jiménez-Luna NE, Niño-Paz JC, et al. Craniofacial Growth Analysis of Individuals With and Without Cleft Lip and Palate in Colombia. Cleft Palate-Craniofacial J Off Publ Am Cleft Palate-Craniofacial Assoc 2022;59:577–88. https://doi.org/10.1177/10556656211013690.

[11] Doğan E, Ergican GÖ, Doğan S. Maxillary Development in Patients with Unilateral Cleft Lip and Palate Compared with Individuals Having Skeletal Class I and Class III Malocclusion. J Clin Pediatr Dent 2021;45:140–5. https://doi.org/10.17796/1053-4625-45.2.12.

[12] Hu Y, Billiau AD, Verdonck A, Wouters C, Carels C. Variation in dentofacial morphology and occlusion in juvenile idiopathic arthritis subjects: A case-control study. Eur J Orthod 2009;31:51–8. https://doi.org/10.1093/ejo/cjn085.

[13] Oye F, Bjornland T, Store G. Mandibular osteotomies in patients with juvenile rheumatoid arthritic disease. Scand J Rheumatol 2003;32:168–73. https://doi.org/10.1080/03009740310002515.

[14] Bezak BJ, Arce KA, Jacob A, Van Ess J. Orthognathic Surgery in Patients with Congenital Myopathies and Congenital Muscular Dystrophies: Case Series and Review of the Literature. J Oral Maxillofac Surg 2016;74:601–9. https://doi.org/10.1016/j.joms.2015.07.023.

Part II

Complications in specific systemic diseases

Article 3

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

Jiqing Li [1]

Sohaib Shujaat [1,2]

Jonas Ver Berne [1]

Eman Shaheen [1]

Constantinus Politis [1]

Reinhilde Jacobs [1,3]

[1] OMFS IMPATH research group, Department of Imaging & Pathology, Faculty of Medicine, KU Leuven and Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium

[2] Department of Maxillofacial Surgery and Diagnostic Sciences, College of Dentistry, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

[3] Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden

Published in:

Oral Diseases. 2022 Oct 27.

3.1 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.

Keywords: rheumatic diseases; orthognathic surgery; complications; infection

3.2 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 labeled 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 [1–3]. 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 [4,5].

Patients suffering from autoimmune rheumatic diseases, such as RA and SLE, are at an increased risk of infection following orthopedic surgery [6–8]. This higher risk might be due to the immunopathogenesis of the disease itself, comorbid conditions, systemic corticosteroid therapy and/or immunosuppressive medications [9–11]. Additionally, RA has been 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 [4,12,13].

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. We hypothesize that patients with rheumatic diseases will be at higher risk of complications following orthognathic surgery compared to healthy patients.

3.3 Materials and Methods

3.3.1 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 following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [14]. 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 mm^2 field of view, 96–110 kV, and a slice thickness of 0.3–0.6 mm [15].

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.

3.3.2 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 [16]), 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 [17]. 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' [18]. The final diagnosis was based on patient history, physical examination, and sensory testing as suggested by Gilron et al. [19]. 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 35 mm 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.

3.3.3 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 the 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.

3.4 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).

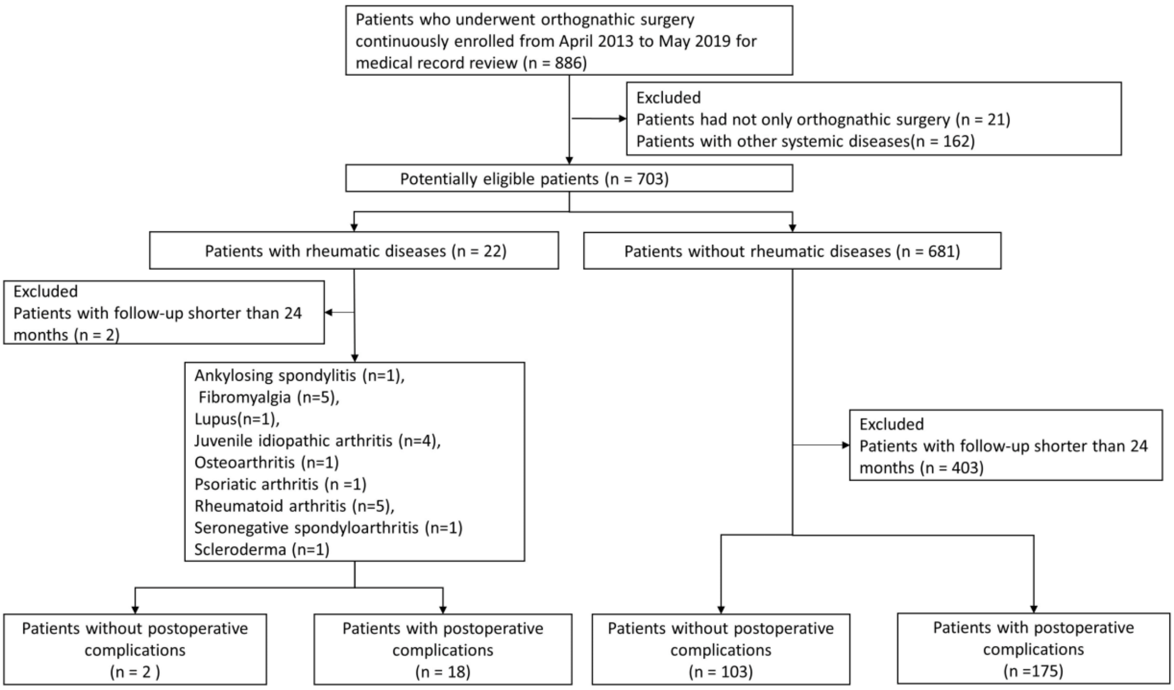


Figure 1. Flowchart of patient selection process.

In 30% (6/20) of rheumatic patients, at least one antirheumatic drug was administered before surgery, which included Methotrexate, Etanercept, and Adalimumab. Drug holidays 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 [20].

Table 1. Baseline Characteristics of healthy and rheumatic patients.

Characteristics	Rheumatic diseases group (n=20)	Control group (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.

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% of 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) were significantly higher in patients with rheumatic diseases compared to healthy patients. In the 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 the healthy group (n=19) only had late-onset infection (mean: 6.2 months, range: 2 weeks - 2 years). There was a significant difference in the 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).

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

Complications	Rheumatic diseases group (n=20)	Control group (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 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 complaints	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 complaints include gender and malocclusion.
N/A: not applicable due to lack of samples.

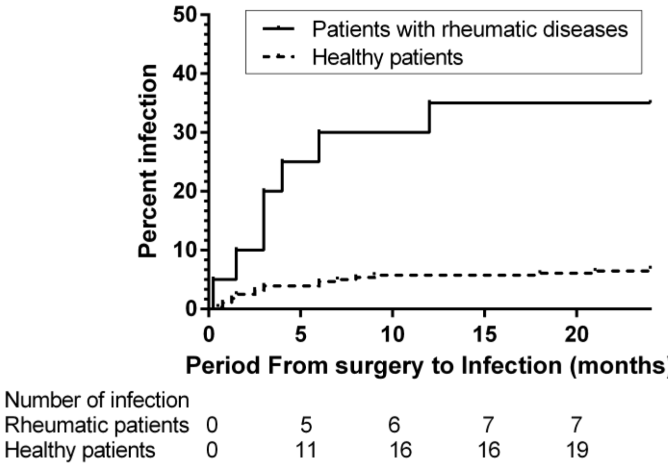


Figure 2. Kaplan-Meier curve for period from surgery till infection (Log-rank p＜0.0001).

3.5 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 [6–8]. 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 [9–11]. 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 is not expected to be influenced by perioperative medical management. Current surgical practice supports continuing conventional synthetic DMARDs (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, and doxycycline) and SLE-specific medications perioperatively [21]. For biologic agents, it is better to stop taking the drugs before surgery and schedule 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 [22]. 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 to infection. These diseases cause impairment of the immune system's ability to respond to novel antigenic stimuli [7]. However, the pathophysiology of rheumatic diseases is complicated involving the interaction of genetic, hormonal, environmental, and immunologic factors [23]. 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 [24–26]. At the same instance, some studies have shown a higher amount of relapse ranging from 21% to 48% following BSSO mandibular advancement in patients with juvenile idiopathic arthritis who also suffered from resorptive TMJ disorders [27,28]. 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 to achieve a stable outcome [29]. 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 toward complications in rheumatic patients.

Although the present study did not show a high risk between rheumatic diseases and postoperative TMJ pain, it is well known that TMJ could 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 [30]. 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 [31]. In the present study, rheumatic diseases were 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 that 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.

3.6 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 postoperative 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 postoperative management of these patients should be established based on detailed recordings of complications and their confounders.

3.7 References

[1] Walsh NC, Crotti TN, Goldring SR, Gravallese EM. Rheumatic diseases: the effects of inflammation on bone. Immunol Rev 2005;208:228–51. https://doi.org/https://doi.org/10.1111/j.0105-2896.2005.00338.x.

[2] Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther 2009;11:229. https://doi.org/10.1186/ar2669.

[3] Sangha O. Epidemiology of rheumatic diseases. Rheumatology 2000;39:3–12. https://doi.org/10.1093/rheumatology/39.suppl_2.3.

[4] Akkara Veetil BM, Bongartz T. Perioperative care for patients with rheumatic diseases. Nat Rev Rheumatol 2012;8:32–41. https://doi.org/10.1038/nrrheum.2011.171.

[5] George MD, Baker JF. Perioperative management of immunosuppression in patients with rheumatoid arthritis. Curr Opin Rheumatol 2019;31:300–6. https://doi.org/10.1097/BOR.0000000000000589.

[6] Baker JF, George MD. Prevention of Infection in the Perioperative Setting in Patients with Rheumatic Disease Treated with Immunosuppression. Curr Rheumatol Rep 2019;21:17. https://doi.org/10.1007/s11926-019-0812-2.

[7] Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population‐based study. Arthritis Rheum 2002;46:2287–93.

[8] Bongartz T, Halligan CS, Osmon DR, Reinalda MS, Bamlet WR, Crowson CS, et al. Incidence and risk factors of prosthetic joint infection after total hip or knee replacement in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2008;59:1713–20. https://doi.org/https://doi.org/10.1002/art.24060.

[9] Mehta B, Pedro S, Ozen G, Kalil A, Wolfe F, Mikuls T, et al. Serious infection risk in rheumatoid arthritis compared with non-inflammatory rheumatic and musculoskeletal diseases: a US national cohort study. RMD Open 2019;5:e000935. https://doi.org/10.1136/rmdopen-2019-000935.

[10] Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy.

Allergy Asthma Clin Immunol 2013;9:30. https://doi.org/10.1186/1710-1492-9-30.
[11] Greenberg JD, Reed G, Kremer JM, Tindall E, Kavanaugh A, Zheng C, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis 2010;69:380–6. https://doi.org/10.1136/ard.2008.089276.
[12] Peters MJ, van der Horst-Bruinsma IE, Dijkmans BA, Nurmohamed MT. Cardiovascular risk profile of patients with spondylarthropathies, particularly ankylosing spondylitis and psoriatic arthritis. Semin. Arthritis Rheum., vol. 34, Elsevier; 2004, p. 585–92.
[13] Meune C, Touzé E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology 2009;48:1309–13.
[14] Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Bull World Health Organ 2007;85:867–72.
[15] Shujaat S, Shaheen E, Politis C, Jacobs R. Three-dimensional evaluation of long-term skeletal relapse following Le Fort I maxillary advancement surgery: a 2-year follow-up study. Int J Oral Maxillofac Surg 2022;51:501–8. https://doi.org/10.1016/j.ijom.2021.07.006.
[16] Angle EH. Classification of malocclusion. Dent Cosm 1899;41:248–264.
[17] Agbaje JO, Salem AS, Lambrichts I, Daems L, Legrand P, Politis C. Intraoperative Computed Tomography in Bilateral Sagittal Split Osteotomy. J Maxillofac Oral Surg 2016;15:461–8. https://doi.org/10.1007/s12663-015-0868-0.
[18] Politis C, Sun Y, Lambrichts I, Agbaje JO. Self-reported hypoesthesia of the lower lip after sagittal split osteotomy. Int J Oral Maxillofac Surg 2013;42:823–9. https://doi.org/10.1016/J.IJOM.2013.03.020.
[19] Gilron I, Watson CPN, Cahill CM, Moulin DE. Neuropathic pain: a practical guide for the clinician. C Can Med Assoc J = J l'Association Medicale Can 2006;175:265–75. https://doi.org/10.1503/cmaj.060146.
[20] Brijs K, Peeters H, Politis C. Orthognathic surgery in patients with systemic diseases. Oral Maxillofac Surg 2022. https://doi.org/10.1007/s10006-022-01054-1.
[21] Goodman SM, George MD. Should we stop or continue conventional synthetic (including glucocorticoids) and targeted DMARDs before surgery in patients with inflammatory rheumatic diseases? RMD Open 2020;6. https://doi.org/10.1136/rmdopen-2020-001214.
[22] Ronald MacKenzie C, Goodman SM, Miller AO. The management of surgery and therapy for

rheumatic disease. Best Pract Res Clin Rheumatol 2018;32:735–49. https://doi.org/https://doi.org/10.1016/j.berh.2019.06.003.

[23] Joseph A, Brasington R, Kahl L, Ranganathan P, Cheng TP, Atkinson J. Immunologic rheumatic disorders. J Allergy Clin Immunol 2010;125:S204–15. https://doi.org/https://doi.org/10.1016/j.jaci.2009.10.067.

[24] Pagnoni M, Amodeo G, Fadda MT, Brauner E, Guarino G, Virciglio P, et al. Juvenile idiopathic/rheumatoid arthritis and orthognathic surgery without mandibular osteotomies in the remittent phase. J Craniofac Surg 2013;24:1940–5. https://doi.org/10.1097/SCS.0b013e31829a8458.

[25] Thaller SR, Cavina C, Kawamoto HK. Treatment of orthognathic problems related to scleroderma. Ann Plast Surg 1990;24:528—533. https://doi.org/10.1097/00000637-199006000-00010.

[26] Leshem D, Tompson B, Britto JA, Forrest CR, Phillips JH. Orthognathic surgery in juvenile rheumatoid arthritis patients. Plast Reconstr Surg 2006;117:1941–6. https://doi.org/10.1097/01.prs.0000209922.46292.58.

[27] Stoor P, Hodzic Z, Arte S. Surgical Treatment of Dentofacial Deformities Caused by Juvenile Idiopathic Arthritis. J Craniofac Surg 2018;29:e51–7. https://doi.org/10.1097/SCS.0000000000004029.

[28] Oye F, Bjornland T, Store G. Mandibular osteotomies in patients with juvenile rheumatoid arthritic disease. Scand J Rheumatol 2003;32:168–73. https://doi.org/10.1080/03009740310002515.

[29] Covert L, Mater H Van, Hechler BL. Comprehensive Management of Rheumatic Diseases Affecting the Temporomandibular Joint. Diagnostics 2021;11. https://doi.org/10.3390/diagnostics11030409.

[30] Helenius LMJ, Hallikainen D, Helenius I, Meurman JH, Könönen M, Leirisalo-Repo M, et al. Clinical and radiographic findings of the temporomandibular joint in patients with various rheumatic diseases. A case-control study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:455–63. https://doi.org/https://doi.org/10.1016/j.tripleo.2004.06.079.

[31] Wolford LM, Reiche-Fischel O, Mehra P. Changes in temporomandibular joint dysfunction after orthognathic surgery. J Oral Maxillofac Surg 2003;61:655–60; discussion 661. https://doi.org/10.1053/joms.2003.50131.

Article 4

Postoperative complications in asthmatic patients following orthognathic surgery: A two-year follow-up study

Jiqing Li [1]
Sohaib Shujaat [1,2]
Eman Shaheen [1]
Jonas Ver Berne [1]
Constantinus Politis [1]
Reinhilde Jacobs [1,3]

[1] OMFS IMPATH research group, Department of Imaging & Pathology, Faculty of Medicine, KU Leuven and Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium
[2] Department of Maxillofacial Surgery and Diagnostic Sciences, College of Dentistry, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[3] Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden

Published in:
Journal of Stomatology, Oral and Maxillofacial Surgery. 2023 Jan 15;124(3):101388.

4.1 Abstract

Background

A lack of evidence exists related to the incidence of postoperative complications in asthmatic patients following orthognathic surgery. The present study aimed to assess the incidence and risk factors of postoperative complications in asthmatic patients following orthognathic surgery.

Material and methods

A retrospective cohort study was conducted which consisted of two groups of patients i.e., asthmatic and systemically healthy patients, who underwent conventional orthognathic surgical procedures (Le Fort I osteotomy, bilateral sagittal split osteotomy, and genioplasty). The recorded postoperative complications in both groups of patients included infection, relapse, altered facial sensation, temporomandibular joint disorders, respiratory complications, and hemorrhage-related events. The association between baseline variables and complications for identifying the possible risk factors was assessed using bivariate analysis and a logistic regression model.

Results

A total of 886 patients underwent orthognathic surgery over a period of 6 years. Following the eligibility criteria, 16 patients were recruited in the asthmatic group and 278 patients were systemically healthy. The most common complications in asthmatic patients were altered sensation (37.5%) followed by TMJ disorder (25.0%) and relapse (18.8%). These patients were associated with an increased risk of relapse (P=0.048) compared to healthy patients. Following adjustment of baseline variables, an increased risk of relapse was still associated with asthma (odds ratio [OR] = 4.704, P = 0.027).

Conclusion

Asthmatic patients suffer from a significantly higher risk of relapse and need to be closely monitored following orthognathic surgery to ensure a stable outcome. Asthma does not seem to have a significant impact on other postoperative complications.

Keywords asthma; orthognathic surgery; complication; relapse

4.2 Introduction

Asthma is a chronic respiratory disorder characterized by variable and recurring symptoms, airway obstruction, inflammation, and hyperresponsiveness [1]. The global World Health Organization (WHO) estimates suggest that it affected approximately 262 million people and caused 461000 deaths in the year 2019 [2]. It is one of the most common coexisting medical diagnoses in patients with dentoskeletal deformities undergoing orthognathic surgical treatment [3].

Previous studies have indicated that asthmatic patients undergoing surgical interventions are at an increased risk of postoperative pulmonary complications compared to the general population, which include pneumonia, bronchospasm, barotrauma, and septicemia [4,5]. Additionally, such patients having neutrophilic airway inflammation suffer from higher levels of systemic inflammation, which negatively impacts the clinical outcomes. This inflammation results from the increase in the circulating proinflammatory cytokines and immune cells [6-8]. Although the higher risk of postoperative adverse events in asthmatic patients is unknown, the impairment of innate and adaptive immune responses and functionality has been suggested as a potential underlying mechanism [9,10]. Furthermore, several perioperative medications such as mivacurium and atracurium have also been linked to pulmonary complications due to their ability to induce allergic reactions through histamine release and further exacerbate respiratory symptoms [11].

To our knowledge, no study exists focusing on the incidence of complications in asthmatic patients following orthognathic surgery. Therefore, the following study was conducted to assess the risk of postoperative complications in asthmatic patients compared to systemically healthy patients following orthognathic surgery. We hypothesized that asthmatic patients would have an increased risk of complications compared to non-asthmatic patients.

4.3 Materials and Methods

4.3.1 Study design and population

A retrospective cohort study was conducted in compliance with the “Strengthening the Reporting of Observational Studies in Epidemiology” (STROBE) statement. Ethical approval was obtained from the Ethical Review Board of the University Hospitals of Leuven (reference number: S66025). Informed consent was not required as patient-specific information was anonymized. The study sample consisted of all systemically healthy and asthmatic patients who underwent conventional orthognathic surgical procedures (Le Fort I osteotomy, bilateral sagittal split osteotomy (BSSO), and genioplasty) for the correction of congenital or acquired dentoskeletal deformities at the Department of Oral and Maxillofacial Surgery, UZ Leuven, Leuven, Belgium, during a 6-year period from April 2013 to May 2019. Exclusion criteria were patients who underwent distraction osteogenesis and a follow-up period of less than 24 months to minimize the risk of detection bias. The patients were divided into two groups i.e., asthmatic patients and systemically healthy patients. All surgeries were performed by the same surgical team and patients were administered with prophylactic antibiotics for a period of 1 week starting on the day of surgery to prevent infection.

4.3.2 Variables

The recorded baseline variables included age, gender, type of malocclusion (Angle classification), orthognathic surgical procedure, and anti-asthmatic medication usage before surgery. The outcome variables were postoperative adverse events, which included, infection, relapse (clinical diagnosis and measurement by the surgeon during regular follow-up), altered facial sensation (hypoesthesia, paresthesia, dysesthesia), temporomandibular joint disorders, respiratory complications, and hemorrhage related event (postoperative bleeding).

4.3.3 Data analyses

Data were analyzed using SPSS statistical software (version 22.0; IBM, Armonk, NY, USA). The normality in the distribution of the continuous data was assessed with the Kolmogorov-Smirnov normality test. Mann–Whitney U test was applied in case the data was not normally distributed. The categorical data were examined using the two-sided chi-square test or Fisher's exact test. Bivariate analysis was conducted to identify the association between asthma and postoperative complications. Following adjustment of the potential confounding factors (age, gender, type of malocclusion, and type of surgery), a logistic regression model was applied for calculating the odds ratios (OR) and their corresponding 95% confidence intervals of postoperative complications between asthmatic and healthy patients. A P-value of < 0.05 was considered statistically significant.

4.4 Results

A total of 886 patients underwent orthognathic surgery over a period of 6-years. Following the eligibility criteria, 294 patients were recruited as illustrated in Figure 1. Out of these, 16 patients belonged to the asthmatic group (mean age ± SD, 26.0±12.3 years) and 278 patients were included in the non-asthmatic control group (mean age ± SD, 25.4±11.3 years). Overall, 9 asthmatic and 175 healthy patients suffered from postoperative complications. Table 1 describes the characteristics of both groups of patients. Five patients (31.3%) in the asthmatic group received at least one of the following anti-asthmatic medications before surgery, leukotriene modifiers, corticosteroids, and bronchodilators.

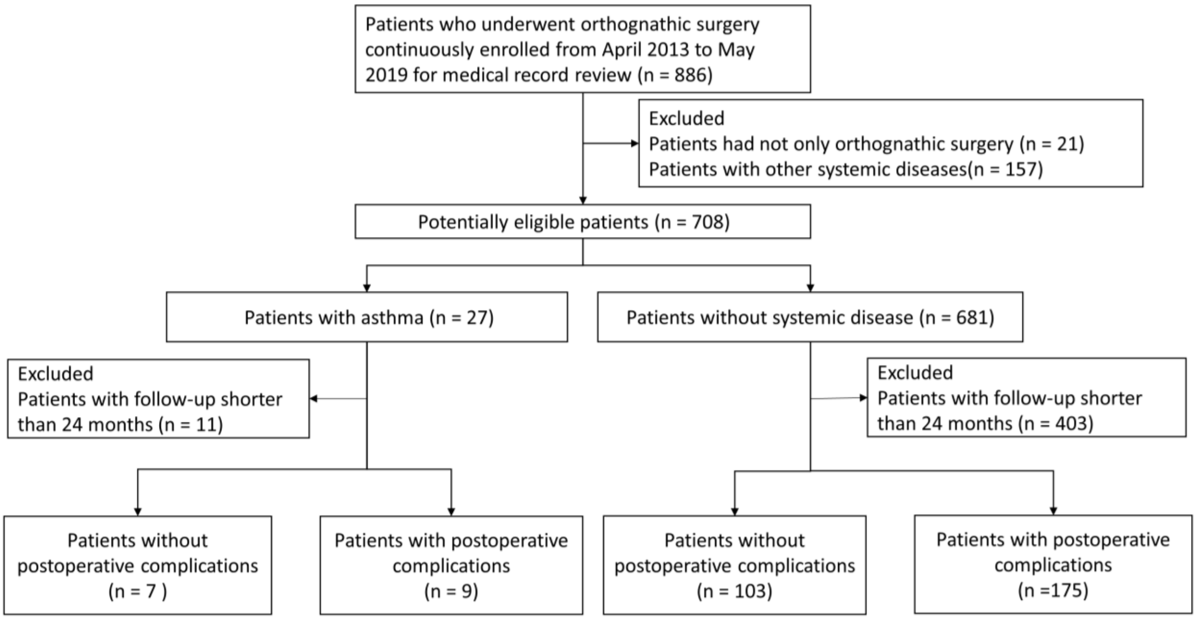


Figure 1. Flowchart of the patient selection process.

Table 1. Baseline characteristics of asthmatic and systemically healthy patients.

Characteristics	Asthmatic patients N=16	Healthy patients N=278	*P*-value
Age, mean (SD), year	25.4 (12.7)	25.8 (11.8)	0.686 [a]
Female sex, No. (%)	10 (62.5)	173 (62.2)	0.539 [b]
Type of malocclusion (%)			0.525 [b]
Class I	0 (0.0)	2 (0.7)	
Class II	14 (87.5)	192 (69.1)	
Class III	2 (12.5)	84 (30.2)	
Type of surgery (%)			
Bimaxillary osteotomy*	6 (37.5)	125 (45.0)	0.596 [b]
BSSO/ genioplasty	8 (50.0)	129 (46.4)	
Le Fort I osteotomy	2 (12.5)	24 (8.6)	
Blood loss, mean (SD), ml	168.1 (82.4)	173.1 (112.2)	
Operation time, mean (SD), h	1.8 (0.8)	2.1 (0.9)	
Anti-asthmatic medication	5 (31.3)	0 (0.0)	/

* Bimaxillary osteotomy involves both Le Fort I osteotomy and BSSO with or without genioplasty.
[a] *P*-value of Mann-Whitney U test; [b] *P*-value of Chi-square test.
Abbreviations: BSSO, Bilateral Sagittal Split Osteotomy.

Table 2 demonstrates the incidence of postoperative complications in both groups of patients. The most common postoperative complication in the asthmatic group was altered sensation (37.5%) followed by TMDs (25.0%) and relapse (18.8%). In addition, 33.3% of asthmatic patients had persistent hypoesthesia complaints at the end of the 24-month follow-up period. Three out of 4 asthmatic patients with TMDs required further non-surgical intervention for the correction of TMJ pain and clicking sounds.

The bivariate association between asthma and postoperative complications showed that asthmatic patients had a significantly higher risk of relapse (*P* = 0.048). Asthma (*P* = 0.048), type of surgery (*P*=0.002), and operation time (*P*=0.009) significantly affected the risk of open bite relapse (Table 3). When logistic regression was applied, asthma maintained a significant association with relapse (odds ratio [OR] = 4.704, CI= 1.191-18.574, *P* = 0.027). No other significant association was detected.

Table 2. Postoperative complication rate in asthmatic and systemically healthy patients.

Complications	Asthmatic patients(N=16)	Healthy patients (N=278)	*P*-value
Infection, n (%)	0 (0)	21 (7.6)	0.615 [a]
Relapse, n (%)	3 (18.8)	13 (4.7)	**0.048** [a]
Altered sensation, n (%)	6 (37.5)	80 (28.8)	0.580 [b]
Temporomandibular joint disorders, n (%)			
TMJ pain	1 (6.3)	18 (6.5)	0.999 [a]
TMJ sound	2 (12.5)	44 (15.8)	0.999 [a]
Non-linear opening path	0 (0)	34 (12.2)	0.231 [a]
Limited opening of the mouth	1(6.3)	12 (4.3)	0.524 [a]
Bleeding-related complications, n (%)	0 (0)	3 (1.1)	0.999 [a]
Postoperative respiratory complications, n (%)	0 (0)	2 (0.7)	0.999 [a]
Removal osteosynthesis material, n (%)	1 (6.3)	72 (25.9)	0.132 [a]
Total, n (%)	9 (56.3)	175 (62.9)	0.836 [b]

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

Table 3. Association between baseline variables and relapse.

Variable	Relapse N=16	No relapse N=278	*P*-value
Age, mean (SD), year	25.4(12.7)	25.5 (11.3)	0.691 [a]
Gender, n			0.581 [b]
Female	11	172	
Man	5	106	
Asthma, n			**0.048** [c]
Yes	3	13	
No	13	265	
Type of surgery, n			**0.002** [b]
Bimaxillary surgery	14	117	
BSSO/ genioplasty	2	135	
Le Fort I osteotomy	0	26	
Type of malocclusion, n			0.590 [b]
Class I	0	2	
Class II	13	193	
Class III	3	83	
Blood loss, mean (SD), ml	168.1 (82.4)	173.1 (112.2)	0.74[a]
Operation time, mean (SD), h	1.8 (0.8)	2.1 (0.9)	**0.009**[a]

[a] *P*-value of Mann-Whitney U test; [b] *P*-value of Chi-square test; [c] *P*-value of Fisher's Exact Test

Abbreviations: BSSO, Bilateral Sagittal Split Osteotomy.

Postoperative open bite relapse occurred in three patients with asthma (Table 4). Two patients required no further surgical intervention for the correction due to a minimal amount of open bite (0.5 mm and 1.0 mm, respectively). However, one patient suffered from an overjet of 6.0 mm and required reoperation. In the control group, 13 patients suffered from anterior open bite and two of them required reoperation due to condylar resorption.

Figure 2 and Figure 3 provide clinical intra-oral photos of patients as examples of asthmatic and non-asthmatic patients with and without relapse at a two-year follow-up time point, respectively. In addition, Figure 4 illustrates three-dimensional visualizations of skeletal relapse in both types of patients.

Table 4. Characteristics of patients with open bite relapse in asthmatic and systematically healthy patients

Groups	N	Gender	Dentofacial diagnosis	Surgical procedure	Relapse diagnosis	Overjet mean±SD (mm)	Open bite mean±SD (mm)
Asthma	3	2 / F 1 / M	3 / Skeletal Class II	3 / Bimaxillary	3 / Anterior open bite	3.33 ± 2.31	-1.16 ± 0.76
Control	13	10 / F 3 / M	10/ Skeletal Class II 3 / Skeletal Class III	12 / Bimaxillary 1 / BSSO	13/ Anterior open bite	4.08 ± 2.11	-2.00 ± 1.21

N, number.

Figure 2 Example of relapse in an asthmatic patient following combined orthodontic and bimaxillary orthognathic surgical correction of skeletal Class II. (A) before orthodontic treatment, (B) before orthognathic surgical treatment, and(C) two years follow-up.

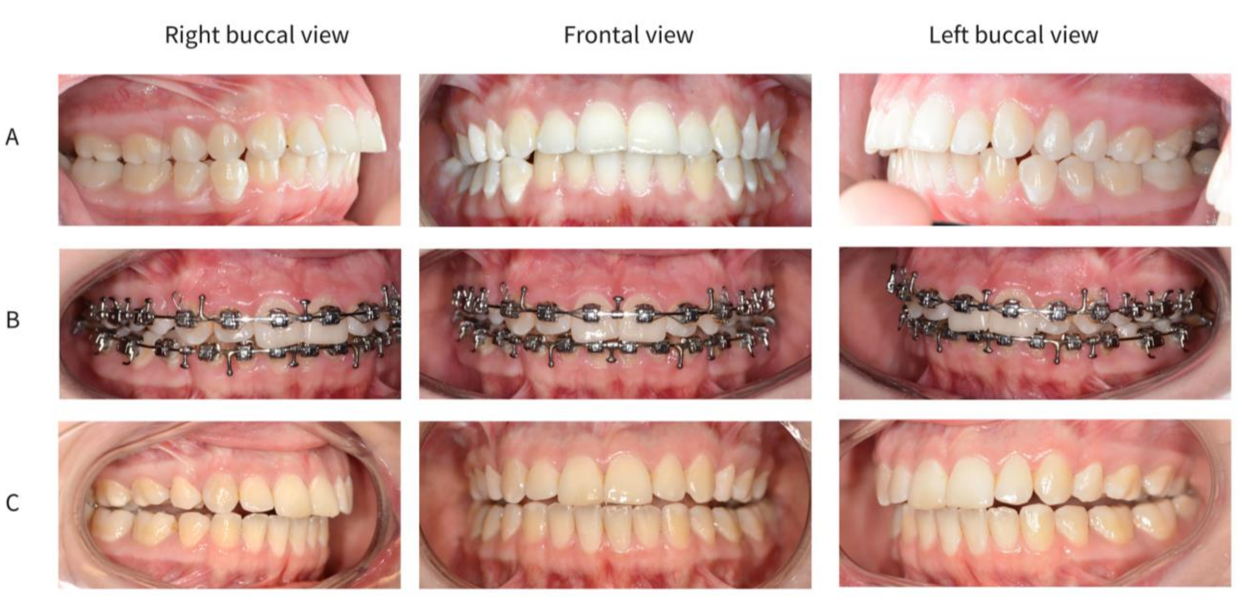


Figure 3 Example of an age- and gender-matched systemically healthy control patient following combined orthodontic and bimaxillary orthognathic surgical correction of skeletal Class II with satisfactory postoperative outcome. (A) before orthognathic surgical treatment, (B) postoperative orthodontic treatment, and (C) two years follow-up.

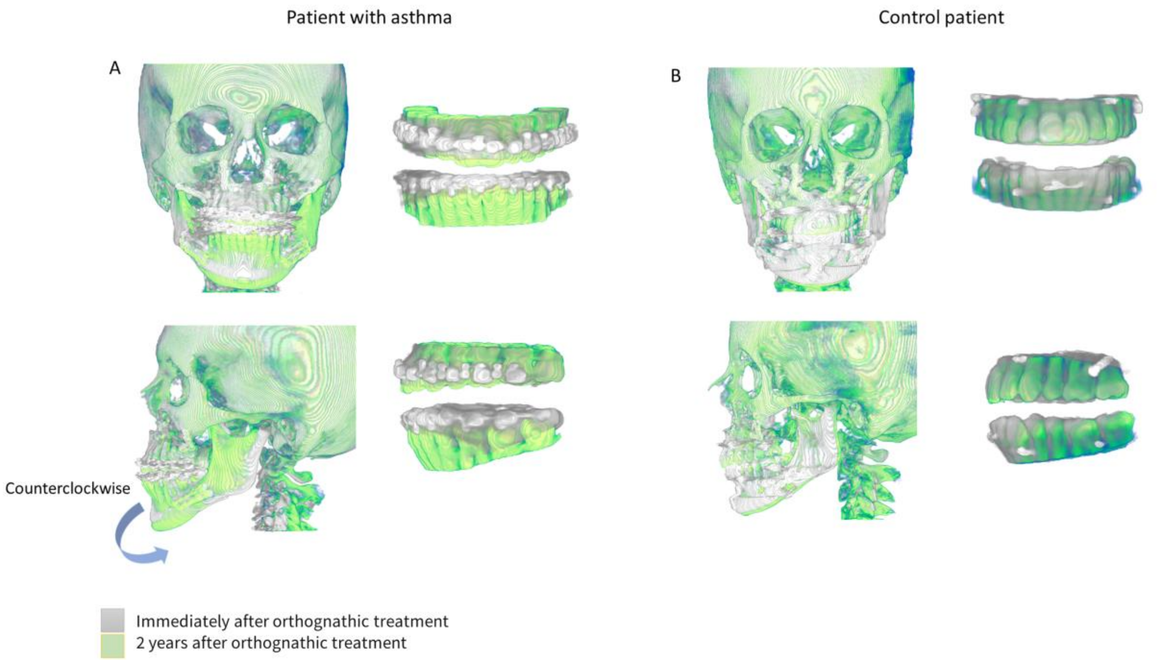


Figure 4 Three-dimensional superimposition of CBCT images illustrating skeletal relapse in asthmatic patient and no relapse in healthy control patient. (A) Maxilla remains stable up to 2 years after surgery, while mandible relapsed counterclockwise in asthmatic patient, and (B) both maxilla and mandible remain stable in healthy control patient.

4.5 Discussion

The following study investigated the risk of postoperative complications in asthmatic patients, where a higher rate of open bite relapse existed in asthmatic patients compared to healthy patients. The maxilla remained relatively stable while the mandible tended to setback. The risk of open bite relapse might have been associated with the increased risk of mouth breathing in asthmatic patients [12]. In addition, the prevalence of allergic rhinitis in such patients is 80% to 90%, which is the main cause of upper airway obstruction and mouth breathing [13]. Mouth breathing remains persistent even following the resolution of anatomical or functional defects either due to neural adaptation, changes in central upper airway control, muscle function, or skeletal alteration. Gomes-Filho et al. reported an association between mouth breathing and asthma in adults with an adjusted OR of 5.21 [14]. Our findings were consistent with those of Wriedt et al., where the authors found a high correlation between mouth breathing which persisted following orthognathic surgical treatment, and open bite relapse with an OR of 12.5 [15]. Hence, it is recommended that the underlying cause of mouth breathing should be removed and myofunctional therapy should be employed in asthmatic patients following orthognathic surgery to help modify the breathing behavior and control the surgical relapse. Another possible reason for open bite relapse could have been associated with root resorption due to a long period administration of drugs such as steroids [16]. It is recommended to perform further prospective case-control studies to three-dimensionally assess skeletal, root and airway changes to identify possible risk factors of relapse in asthmatic patients.

In the present study, no significant association existed between asthma and TMDs, which was consistent with a previous study [17]. At the same instance, other studies reported a higher risk of TMDs in asthmatic patients, where the authors hypothesized that it might be a risk factor for TMDs due to the presence of a common immune response that releases similar proinflammatory cytokines in both diseases [18,19]. This conflicting evidence might have been associated with a small sample of asthmatic patients in our study and the findings should be interpreted with caution. Further studies with a larger sample size are required to confirm the association between asthma and TMDs.

Although no postoperative respiratory complications occurred in asthmatic patients, these patients are still considered to be at a higher risk of pulmonary complications during the perioperative period, which might lead to serious postoperative morbidity [4,20]. Hence, oral corticosteroids and bronchodilators should be administered in asthmatic patients preoperatively which are well-tolerated with a low incidence of adverse effects and reduce the possibility of pulmonary complications [21].

The primary strength of the present study was the reporting of complications in asthmatic patients who underwent orthognathic surgical procedures with a follow-up period of 24 months, which has not been previously investigated. Nevertheless, the study had several limitations. Firstly, owing to the retrospective nature of the study, the possibility of unknown confounding factors cannot be ruled out. Secondly, the results should be interpreted with caution due to a limited sample size of asthmatic patients. Thirdly, the study was conducted in a tertiary care center, which might influence the generalizability of the findings as the included patients were not a representative of the general population with asthma who might suffer from more coexisting conditions and a higher complication rate. Finally, the results were not analyzed based on the severity of asthma, which might have further created bias within our findings.

4.6 Conclusion

Asthmatic patients are at a significantly higher risk of open bite recurrence following orthognathic surgery and should be closely monitored to ensure a stable outcome. Furthermore, no significant association existed between asthma and infection, altered sensation, TMDs, bleeding-related complications, or respiratory complications. Although these findings update the current knowledge related to the complications in orthognathic surgery patients with systemic comorbidities, it is recommended to conduct future well-designed prospective studies with a large sample size to reach a better understanding of the asthma-related relapse.

4.7 References

[1] Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol 2007;120:S94-138. https://doi.org/10.1016/j.jaci.2007.09.043.

[2] Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1204–22. https://doi.org/10.1016/S0140-6736(20)30925-9.

[3] Cunningham SJ, Moles DR. A national review of mandibular orthognathic surgery activity in the National Health Service in England over a nine year period: Part 2 - patient factors. Br J Oral Maxillofac Surg 2009;47:274–8. https://doi.org/https://doi.org/10.1016/j.bjoms.2008.10.019.

[4] Lin C-S, Chang C-C, Yeh C-C, Chung C-L, Chen T-L, Liao C-C. Postoperative Adverse Outcomes in Patients With Asthma: A Nationwide Population-based Cohort Study. Medicine

(Baltimore) 2016;95:e2548–e2548. https://doi.org/10.1097/MD.0000000000002548.

[5] Numata T, Nakayama K, Fujii S, Yumino Y, Saito N, Yoshida M, et al. Risk factors of postoperative pulmonary complications in patients with asthma and COPD. BMC Pulm Med 2018;18:4. https://doi.org/10.1186/s12890-017-0570-8.

[6] Wood LG, Baines KJ, Fu J, Scott HA, Gibson PG. The Neutrophilic Inflammatory Phenotype Is Associated With Systemic Inflammation in Asthma. Chest 2012;142:86–93. https://doi.org/https://doi.org/10.1378/chest.11-1838.

[7] Takemura M, Matsumoto H, Niimi A, Ueda T, Matsuoka H, Yamaguchi M, et al. High sensitivity C-reactive protein in asthma. Eur Respir J 2006;27:908–12. https://doi.org/10.1183/09031936.06.00114405.

[8] Brüünsgaard H, Pedersen BK. Age-related inflammatory cytokines and disease. Immunol Allergy Clin North Am 2003;23:15–39. https://doi.org/10.1016/S0889-8561(02)00056-5.

[9] Contoli M, Message SD, Laza-Stanca V, Edwards MR, Wark PAB, Bartlett NW, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. Nat Med 2006;12:1023–6. https://doi.org/10.1038/nm1462.

[10] Wark PAB, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med 2005;201:937–47. https://doi.org/10.1084/jem.20041901.

[11] Hepner DL, Castells MC. Anaphylaxis during the perioperative period. Anesth Analg 2003;97:1381–95. https://doi.org/10.1213/01.ane.0000082993.84883.7d.

[12] Izuhara Y, Matsumoto H, Nagasaki T, Kanemitsu Y, Murase K, Ito I, et al. Mouth breathing, another risk factor for asthma: the Nagahama Study. Allergy 2016;71:1031–6. https://doi.org/https://doi.org/10.1111/all.12885.

[13] Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. J Allergy Clin Immunol 2000;106:S201-5. https://doi.org/10.1067/mai.2000.110151.

[14] Gomes-Filho IS, Soledade-Marques KR, Seixas da Cruz S, de Santana Passos-Soares J, Trindade SC, Souza-Machado A, et al. Does periodontal infection have an effect on severe asthma in adults? J Periodontol 2014;85:e179-87. https://doi.org/10.1902/jop.2013.130509.

[15] Wriedt S, Buhl V, Al-Nawas B, Wehrbein H. Combined Treatment of Open Bite – Long-term Evaluation and Relapse Factors. J Orofac Orthop / Fortschritte Der Kieferorthopädie 2009;70:318–26. https://doi.org/10.1007/s00056-009-9912-3.

[16] Krishnan V, Davidovitch Z. Integrated clinical orthodontics. John Wiley & Sons; 2012.

[17] Nishioka M, Ioi H, Matsumoto R, Goto TK, Nakata S, Nakasima A, et al. TMJ osteoarthritis/osteoarthrosis and immune system factors in a Japanese sample. Angle Orthod 2008;78:793–8.

[18] Fredricson AS, Khodabandehlou F, Weiner CK, Naimi-Akbar A, Adami J, Rosén A. Are there early signs that predict development of temporomandibular joint disease? J Oral Sci 2018;60:194–200. https://doi.org/10.2334/josnusd.17-0073.

[19] Song H-S, Shin J-S, Lee J, Lee YJ, Kim M, Cho J-H, et al. Association between temporomandibular disorders, chronic diseases, and ophthalmologic and otolaryngologic disorders in Korean adults: A cross-sectional study. PLoS One 2018;13:e0191336.

[20] Warner DO, Warner MA, Barnes RD, Offord KP, Schroeder DR, Gray DT, et al. Perioperative respiratory complications in patients with asthma. Anesthesiology 1996;85:460–7. https://doi.org/10.1097/00000542-199609000-00003.

[21] Tirumalasetty J, Grammer LC. Asthma, Surgery, and General Anesthesia: A Review. J Asthma 2006;43:251–4. https://doi.org/10.1080/02770900600643162.

Article 5

Autoimmune diseases and orthognathic surgery: a case series of 12 patients

Jiqing Li [1]

Sohaib Shujaat [1,2]

Eman Shaheen [1]

Constantinus Politis [1]

Reinhilde Jacobs [1,3]

[1] OMFS IMPATH research group, Department of Imaging & Pathology, Faculty of Medicine, KU Leuven and Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium

[2] Department of Maxillofacial Surgery and Diagnostic Sciences, College of Dentistry, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

[3] Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden

Published in:

Journal of Plastic, Reconstructive & Aesthetic Surgery. 2023 Jun 9.

5.1 Abstract

Autoimmune diseases result from the immune system attacking native cells and tissues due to the recognition of "self" antigen as a foreign antigen. This group of disorders is associated with an increased risk of complications following surgical interventions, as the immune system might cause tissue destruction. The study aimed to investigate the risk of surgical complications in patients with autoimmune diseases, who are at a higher risk of complications due to their condition. Among 886 patients who underwent orthognathic surgery, 12 types of autoimmune diseases in 22 patients were identified. For this case-series study, 12 patients were selected with a follow-up period of at least two years. The surgical procedures were executed by a single surgical team, which involved single or multi-piece Le Fort I osteotomy, Hunsuck/Epker modification of bilateral sagittal split osteotomy (BSSO), and/or genioplasty. The recorded outcome variables were postoperative adverse events, which included respiratory or blood-related complications, wound infection, neurosensory disturbances, temporomandibular joint complications, and relapse. Only two patients recovered from surgery without any post-operative complications, while others suffered from delayed recovery from neurosensory disturbance (5/12), infection (5/12), TMJ complications (2/12), and other complications. The findings of this study suggest that patients with autoimmune diseases undergoing orthognathic surgery are at higher risk of complications, highlighting the importance of careful consideration of patient selection and risk stratification prior to surgical intervention. The study also emphasizes the importance of close postoperative follow-up to detect and manage complications promptly.

Keywords: Case series; Autoimmune diseases; Orthognathic surgery; Complications.

5.2 Introduction

Autoimmune diseases consist of a group of disorders in which “self” antigen is mistakenly recognized as a foreign antigen, and autoantibodies are produced for the attack against native cells of tissues and organs [1]. So far, around 80 autoimmune diseases have been identified in the literature, which commonly include type 1 diabetes mellitus, multiple sclerosis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren's syndrome. The incidence of autoimmune diseases varies based on geographical regions with approximately 4% of the world population being affected by one of the autoimmune diseases and women are at a higher risk compared to men [2]. Prior contemporary theories have suggested that genetic predisposition and environmental factors trigger the development of autoimmune diseases which ultimately trigger the immune pathways to cause tissue destruction [3].

Considering the nature of autoimmune diseases, the risk of complications following surgical interventions is also higher compared to medically fit patients. For instance, prior studies have reported that rheumatic patients who underwent orthognathic surgery were at a higher risk of postoperative infection. Furthermore, rheumatic diseases have also been strongly associated with an increased cardiovascular risk and also result in altered coagulation due to the presence of antiphospholipid antibodies [4–6]. In another study, patients with end-stage liver disease caused by an autoimmune process had a greater risk of perioperative thrombotic complications following orthotopic liver transplantation [7].

Although autoimmune diseases in patients undergoing orthognathic surgery are relatively rare, one cannot ignore the increased possibility of surgical complications and how to manage them. The complications following orthognathic surgery in medically fit patients have been comprehensively reported, and a surgeon has a thorough understanding of the involved risks and their management protocols. However, little is known about the outcomes and risk of complications in patients suffering from different autoimmune diseases.

Therefore, the following case series aimed to investigate the surgical outcomes and complications following orthognathic surgery in patients with different autoimmune diseases.

5.3 Materials and Methods

This retrospective study was conducted in compliance with the World Medical Association Declaration of Helsinki on medical research. Ethics approval was granted by the Ethics Committee of the University Hospitals/Catholic University Leuven (S66025). Patient-specific information was anonymized.

Patients who had undergone orthognathic surgery from April 2013 to February 2022 were identified from the database of the Department of Oral and Maxillofacial Surgery, UZ Leuven, Belgium. Inclusion criteria consisted of patients diagnosed with autoimmune diseases who underwent orthognathic surgical correction of dentoskeletal deformities and had minimum follow-up period of 2 years. Patients with craniofacial anomalies such as cleft lip and/or palate, hemifacial microsomia, craniosynostosis and other syndrome anomalies were excluded.

All surgical procedures were executed by a single surgical team, which involved single or multi-piece Le Fort I osteotomy, Hunsuck/Epker modification of bilateral sagittal split osteotomy (BSSO), and/or genioplasty. Rigid fixation of LF I and BSSO was performed using titanium miniplates with screws, while genioplasty was stabilized using a chin plate (KLS Martin GmbH, Freiburg, Germany). Anterior iliac crest bone graft was interposed in between the osteotomy lines when a visible bone gap existed [8]. Depending on the age of the patient and the size of the bone gap, a dicalcium phosphate synthetic bone graft (CopiOs® Bone Void Filler) was also used without fixation in order to support bone formation and prevent bony defect at the lower mandibular border [9]. Antibiotics were administered to prevent infection for approximately one week following surgery [10].

The recorded outcome variables were postoperative adverse events, which included respiratory or blood-related complications, wound infection, neurosensory disturbances, temporomandibular joint (TMJ) complications (pain, abnormal sounds, non-linear opening or closing path, limited mouth opening), and relapse. The detailed description and investigation of included complications were in accordance with a prior study [10].

Pre- and post-operative cone-beam computed tomography (CBCT) images were acquired for all patients using either Planmeca Promax 3D Max (Planmeca, Helsinki, Finland) or Newtom VGi-evo (Newtom, Verona, Italy) CBCT devices with standardized scanning parameters of 230 × 260 - 240 × 190 mm^2 field of view, 96–110 kV, and a slice thickness of 0.3–0.6 mm [9]. Panoramic and cephalometric radiography was performed with one of the following devices: Cranex Tome (Soredex, Finland), Veraviewpocs 2D (J. Morita, USA), Planmeca Promax 2D (Planmeca Oy, Finland), and Vistapano S (Durr Dental AG, Germany).

In addition, tooth contact, bite force, and interrelationship of occlusal surfaces were recorded and measured by T-scan (T-Scan III, Software version 8.0.1, Tekscan, Inc., Boston, MA, USA), a digital occlusion analysis system which uses pressure-sensitive, thin bite transducer embedded in a dental arch-shaped sensor [11].

5.4 Results

From a total pool of 886 patients who underwent orthognathic surgery, 12 patients were identified with different types of autoimmune diseases (mean age ± SD, 31.9 ± 13.4 years). The mean follow-up time was 27.5 months. Clinical characteristics of these patients are described in Table 1. Only two patients recovered from surgery without any post-operative complications, while others suffered from delayed recovery from neurosensory disturbance (5/12), infection (5/12), and TMJ complications (2/12). Five patients were taking immunosuppressive drugs prior to orthognathic treatment. The average blood loss during the operation was 103 ± 108 ml and the mean surgery duration was 1.8 ± 0.9 hours.

Case histories (see Table 1 for detailed patient characteristics)

5.4.1 Patient 1 (celiac disease)

A 16-year-old male patient with celiac disease underwent BSSO advancement to correct Class II malocclusion. The operation went well and the patient completely recovered from postoperative hypoesthesia within three months. During the first-year postoperative visit, the patient reported bilateral grating TMJ sounds upon maximal mouth opening. By the end of 2^{nd} year follow-up, the right-side sound persisted without any other symptoms, and no further treatment was required. Both occlusal and skeletal outcomes were satisfactory. (Figure 1 and Figure 2).

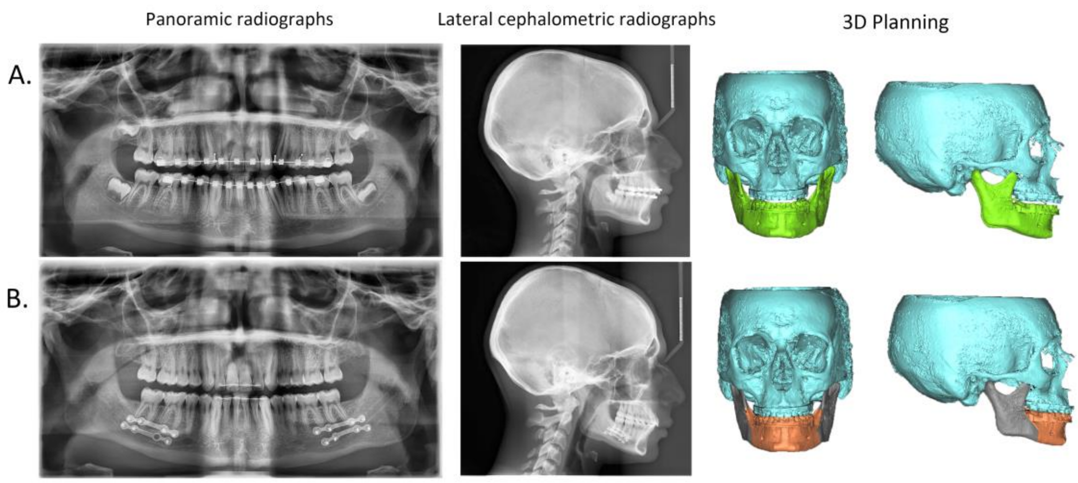


Figure 1. Panoramic and lateral cephalometric imaging with three-dimensional (3D) virtual modeling. A. Preoperative radiographs and virtual model. B. Two-year postoperative radiographs and 3D virtual plan.

Figure 2. Intraoral photographs, A. Preoperative. B. Two-year postoperative.

5.4.2 Patient 2 (systemic lupus erythematosus)

A 36-year-old female patient with systemic lupus erythematosus underwent tri-piece LF I osteotomy and BSSO advancement for the correction of traumatic deep bite and Class II malocclusion. At 6th week postoperative visit, the patient complained of bilateral TMJ pain, which was more severe on the left side. Pain due to normal surgical recovery or orthodontic treatment was ruled out, and physiotherapy was initiated at 7th month following surgery which was effective in reducing pain. However, the pain started to reoccur following completion of physiotherapy. In addition, a creaking sound was also detected at the level of the left TMJ. By the end of 2nd year follow-up visit, a CBCT scan was acquired, revealing early signs of left condylar osteoarthrosis (Figure 3). The maxillary titanium plates were removed due to palpability. Both occlusal and skeletal outcomes were satisfactory, and the patient is currently undergoing follow-up for TMJ evaluation (Figure 4 and Figure 5).

Figure 3. CBCT imaging. A. Preoperative normal condyle. B. Early osteoarthrosis signs of left condyle at 2 years follow-up.

Figure 4. Intraoral photographs. A. Preoperative. B. Two-year postoperative.

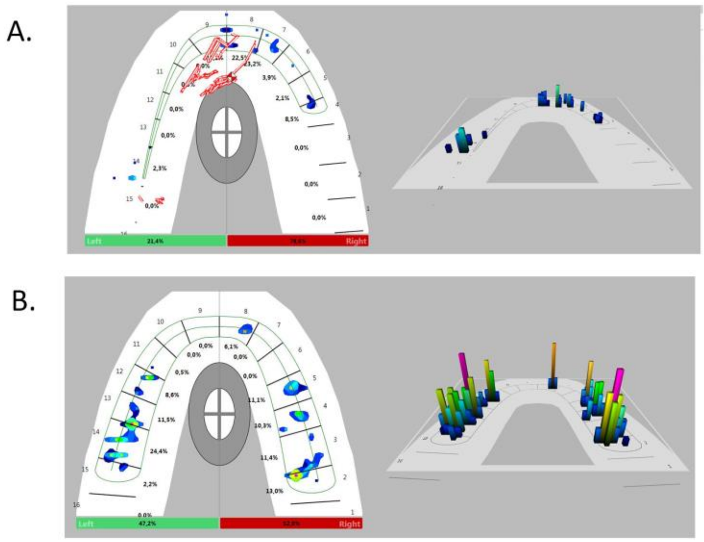


Figure 5. Occlusion patterns and force distribution. A. Preoperative bilateral posterior open bite. B. Normal occlusion after bimaxillary surgery.

5.4.3 Patient 3 (oligoarticular juvenile idiopathic arthritis)

A 25-year-old female patient, diagnosed with oligoarticular juvenile idiopathic arthritis at the age of 15, underwent bimaxillary surgery and genioplasty to correct vertical excess and Class II malocclusion. At the time of surgery, the patient was in remission, which was the ideal time for the procedure. The patient discontinued Methotrexate and Etanercept two and three weeks before surgery, respectively, and resumed these medications 4-6 weeks following surgery. Additionally, the patient received minocycline, glucosamine, and curcumin from 3 months before surgery to 3 months after the procedure. Three months after the surgical procedure, a Vitamin B-complex supplement (Neurobion®) was prescribed due to hypoesthesia in the lower jaw. At the 20-month follow-up, a painful fistula without pus outflow was detected in the right posterior vestibular region, leading to the removal of osteosynthesis material in this area (Figure 6). At the two-year follow-up, the sensation in the lower jaw was normal, except for hypoesthesia in the chin region. Both occlusal and skeletal outcomes were satisfactory.

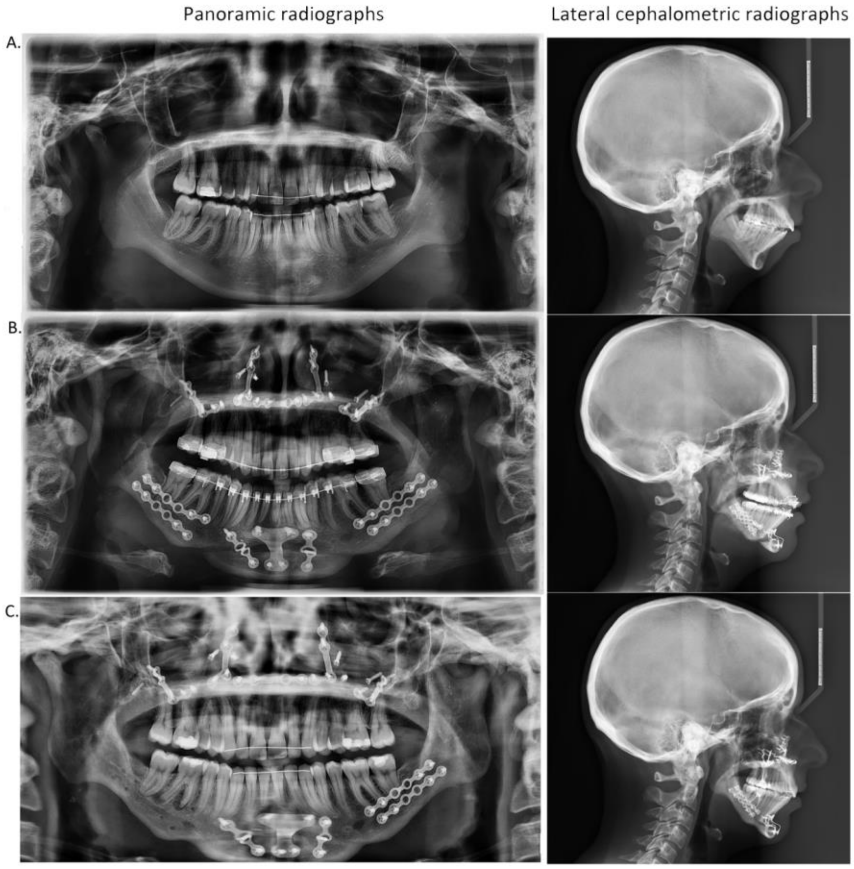


Figure 6. Panoramic and lateral cephalometric imaging. A. preoperative. B. One-year postoperative. C. Two-years postoperative.

5.4.4 Patient 4 (rheumatoid arthritis)

A 51-year-old female patient with rheumatoid arthritis underwent bimaxillary surgery for the correction of Class II malocclusion and obstructive sleep apnea. Patient smoked an average of four cigarettes per day and was taking Leflunomide and Adalimumab for rheumatism. Adalimumab was discontinued 1.5 months prior to surgery in consultation with the rheumatologist. Both TMJs were normal. Minocycline, glucosamine, and curcumin were administered from 3 months before surgery untill 3 months after the surgery. At 1 month following surgery, the patient experienced pain and swelling in the left maxillary region, for which Clindamycin 300mg 3x/day for 1 week was administered, resulting in complete resolution. However, the patient subsequently developed painless swelling with pus discharge in the maxillary left anterior vestibular region (Figure 7). At 4 months postoperatively, incision and drainage of pus with removal of a completely loose plate was performed. During the procedure, another fistula opening was identified in the vestibular region of the right lateral incisor. Subsequently, surgical exploration was conducted, resulting in the removal of two plates that were loose and surrounded by pus (Figure 8.C). Ten months later, the patient experienced recurrent swelling in the left upper jaw, requiring several courses of antibiotics. The remaining osteosynthesis materials in the second quadrant were removed. At one year postoperatively, the patient was diagnosed with a surgical ciliary cyst based on history and radiological images (Figure 8.D). Both occlusal and skeletal outcomes were satisfactory, with no further complications.

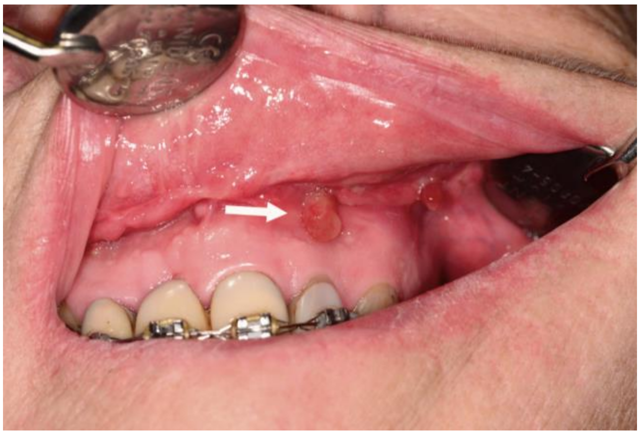


Figure 7. Postoperative infection with pus discharge at 2 months.

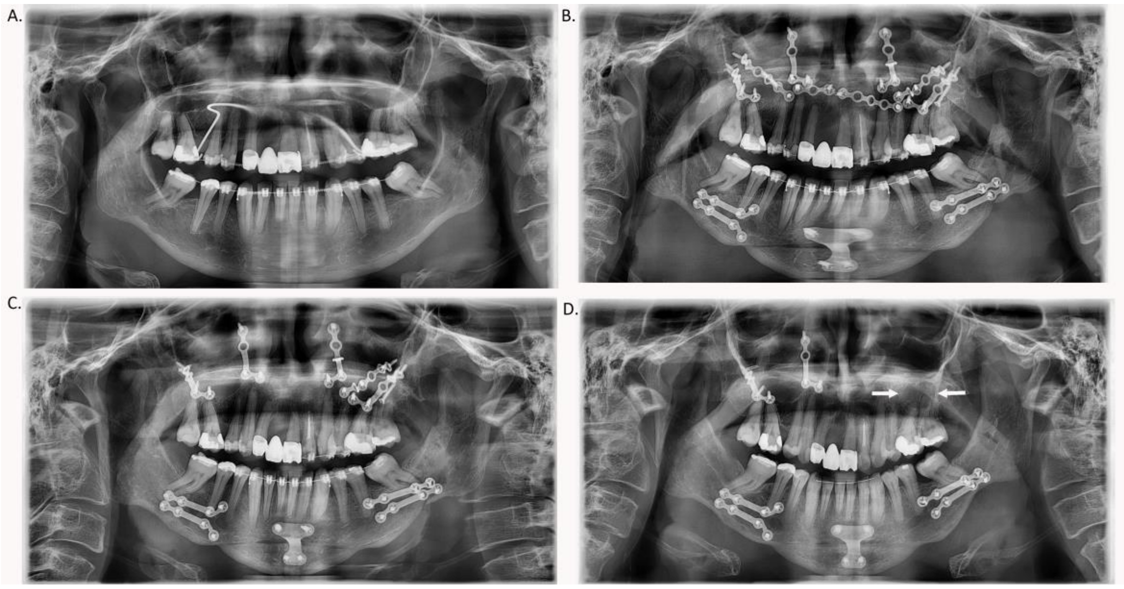


Figure 8. Panoramic radiographs. A. Preoperative. B. One-month postoperative. C. Four-month postoperative. D. One year postoperative showing surgical ciliary cyst.

5.4.5 Patient 5 (multiple sclerosis)

A 30-year-old female patient with multiple sclerosis underwent bimaxillary surgery to correct Class

III malocclusion and TMJ pain (Figure 9). During the first postoperative night, the patient experienced an episode of pain and hyperventilation, which rapidly resolved on the same day. At 3 weeks post-surgery, persistent swelling and pain were noted in the left posterior mandibular region. Despite several courses of antibiotics and facial lymphatic drainage, the infection did not resolve. Consequently, the plates and screws were removed at the 6th month postoperatively. During the removal of the osteosynthesis material, a mobile necrotic piece of bone was found posteriorly and was also removed (Figure 10). Ten months later, the remaining osteosynthesis material was also removed due to hypersensitivity. Both occlusal and skeletal outcomes were satisfactory, and no further complications were reported during follow-up.

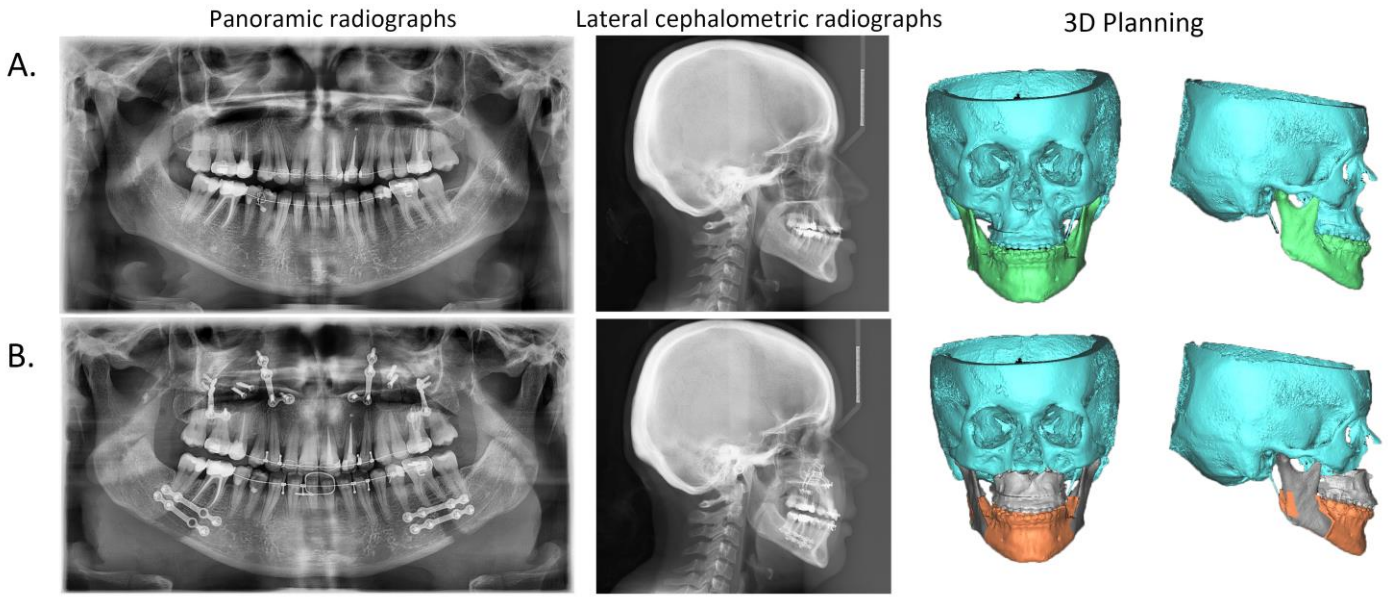


Figure 9. Panoramic and lateral cephalometric imaging with three-dimensional (3D) virtual modeling A. Preoperative radiographs and virtual model. B. Two-year postoperative radiographs and 3D virtual plan.

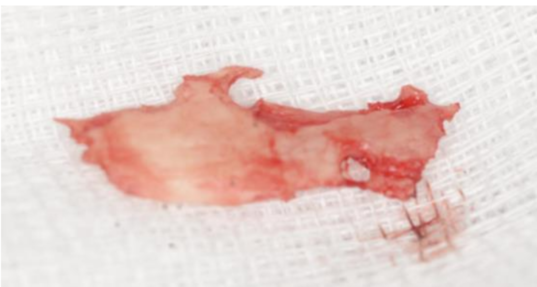


Figure 10. Piece of removed necrotic bone.

5.4.6 Patient 6 (diabetes mellitus type 1)

A 30-year-old female patient with controlled diabetes mellitus type 1 underwent LF I osteotomy for the correction of Class II malocclusion and obstructive sleep apnea. Patient also had a history of juvenile idiopathic arthritis, but the rheumatoid factor was zero, indicating no active inflammation. Based on the history of juvenile idiopathic arthritis, Minocycline 50 mg was started one month preoperatively to 3 months postoperatively. At the end of the 2-year follow-up period, the patient reported limited hypoesthesia in the left side of the upper and lower lip, with intermittent paresthesia. However, this condition did not significantly affect the patient's daily activities. The surgery successfully corrected sleep apnea, as confirmed by a sleep lab study. Both occlusal and skeletal outcomes were satisfactory (Figure 11).

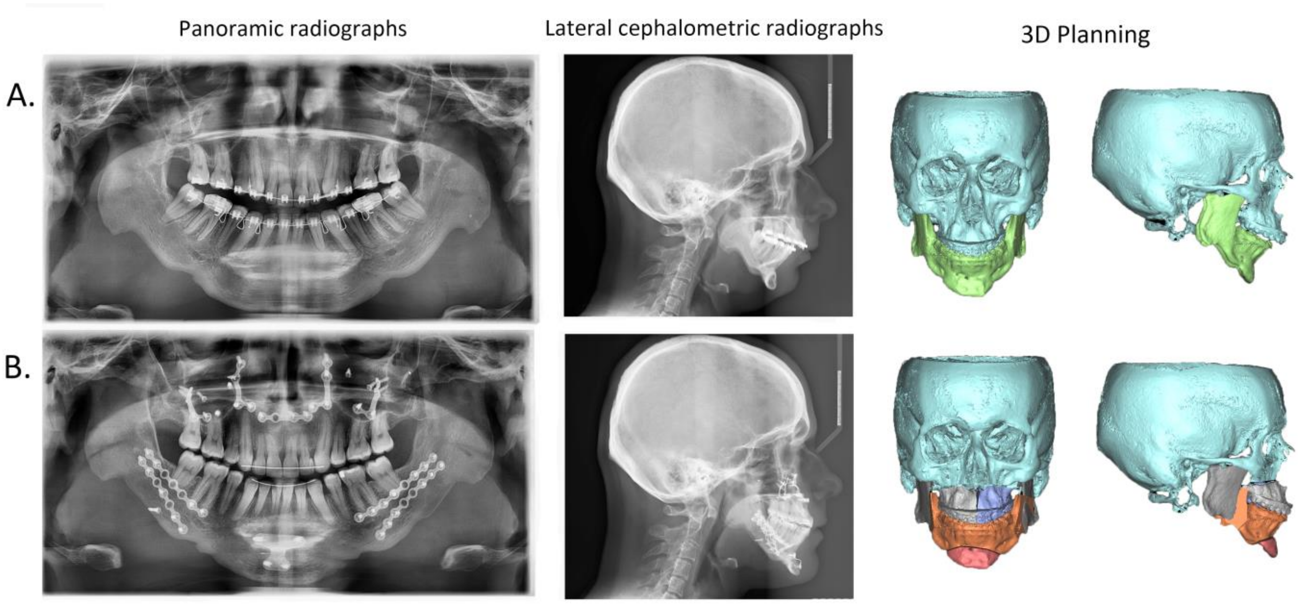


Figure 11. Panoramic and lateral cephalometric imaging with three-dimensional (3D) virtual modeling. A. Preoperative radiographs and virtual model. B. Two-year postoperative radiographs and 3D virtual plan.

5.4.7 Patient 7 (scleroderma)

A 19-year-old female patient, diagnosed with scleroderma at the age of 13, underwent BSSO advancement to correct severe Class II malocclusion (Figure 12). The patient was receiving treatment for scleroderma with Methotrexate and cortisone. Methotrexate was stopped 3 weeks before the surgical procedure and restarted 6 weeks postoperatively. Additionally, minocycline (50 mg) was started 1 month before the procedure till 3 months postoperatively. At 6 months postoperatively, patient suffered from cracking sounds with accompanying pain in the left TMJ, which resolved by the 1-year postoperative mark. At the 2-year follow-up, the patient still had residual hypoesthesia in the left and right sides of the lower lip and chin. As a result, osteosynthesis material was removed, and vitamin B-complex supplement was prescribed for 2 months. Currently, the hypoesthesia complaints are limited to the chin region and the patient continues to be monitored (Figure 13). Both occlusal and skeletal outcomes were satisfactory.

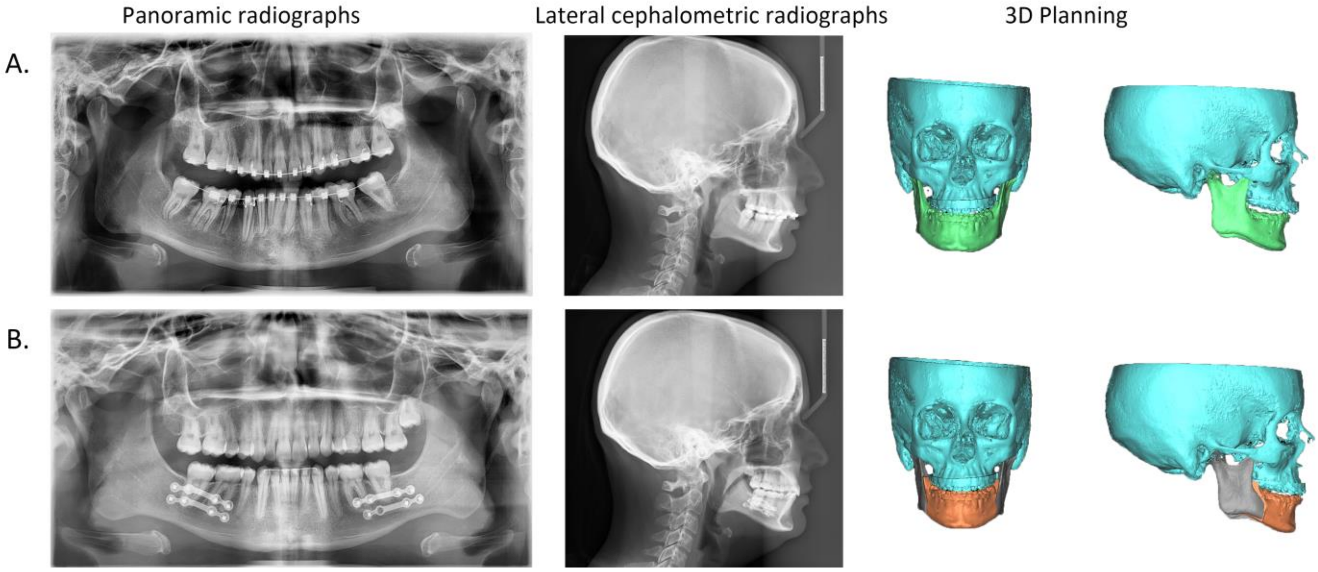


Figure 12. Panoramic and lateral cephalometric imaging with three-dimensional (3D) virtual modeling. A. Preoperative radiographs and virtual model. B. Two-year postoperative radiographs and 3D virtual plan.

Figure 13. Region having hypoesthesia at 3 years postoperatively.

5.4.8 Patient 8 (psoriasis)

A 27-year-old male patient diagnosed with psoriasis underwent bimaxillary surgery to correct maxillary hypoplasia and anterior overbite. The surgery was successful, and sensory feedback completely recovered by the one-year follow-up. Bite force, as measured by the T-scan, showed improvement following the surgery (Figure 14). Both occlusal and skeletal outcomes were satisfactory, with no complications reported during follow-up (Figure 15 and Figure 16).

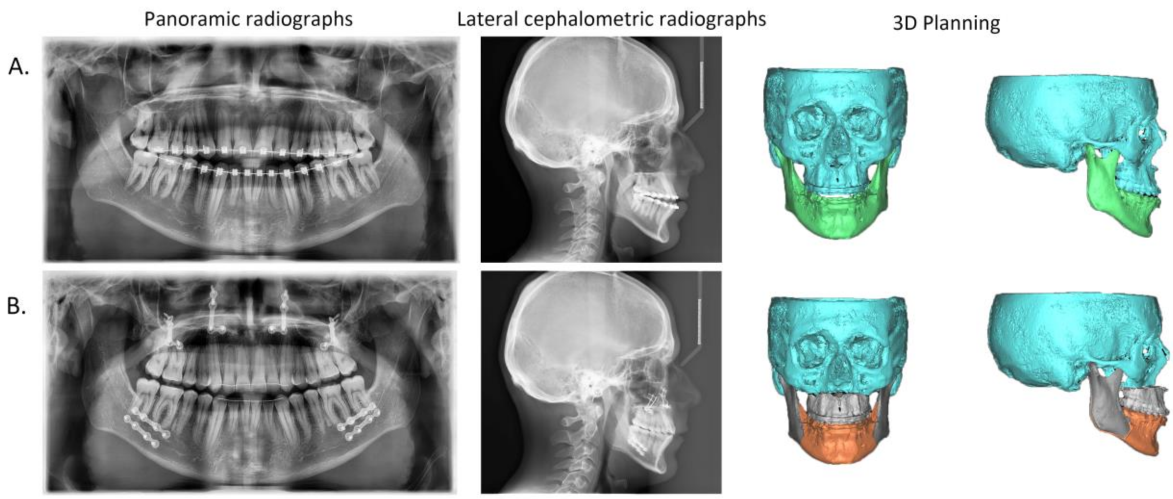


Figure 14. Panoramic and lateral cephalometric imaging with three-dimensional (3D) virtual modeling. A. Preoperative radiographs and virtual model. B. Two-year postoperative radiographs and 3D virtual plan.

Figure 15. Intraoral photographs. A. Preoperative. B. Two-year postoperative.

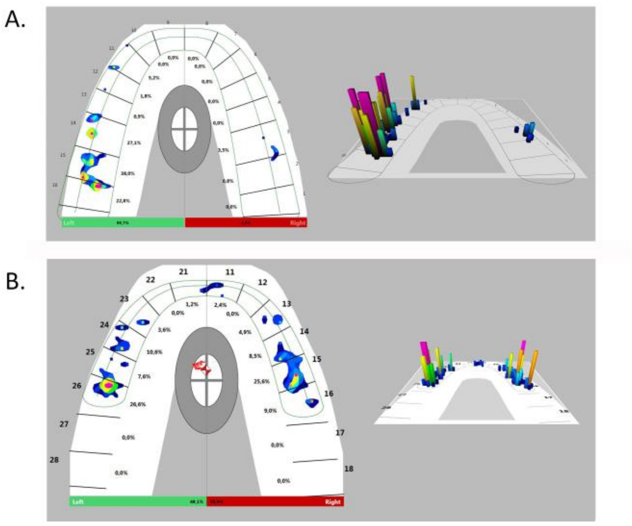


Figure 16. Occlusion patterns and force distribution. A. Preoperative anterior open bite. B. Normal occlusion after bimaxillary surgery.

5.4.9 Patient 9 (Ehler-Danlos syndrome)

A 40-year-old male patient diagnosed with Ehler-Danlos syndrome, underwent BSSO and genioplasty to correct Class II malocclusion and crossbite. The patient had a previous diagnosis of complete anterior disc dislocation without reduction in the TMJ. Despite ongoing conservative TMJ treatment and arthroscopy, the patient experienced persistent pain and limited mouth opening. At 6 weeks following the surgical procedure, signs of infection and pus were observed in the intraoral wounds of the BSSO. The patient was prescribed clindamycin 600mg three times a day. As the infection persisted, the decision was made to remove the osteosynthesis material from the BSSO area three months postoperatively. At the 2-year follow-up, a CBCT image revealed signs of osteoarthrosis in the right TMJ (Figure 17). Three years after surgery, the patient had a stable occlusion with normal mouth opening (25mm) and no TMJ pain. Limited hypoesthesia of the lower lip still exists, but it does not significantly bother the patient.

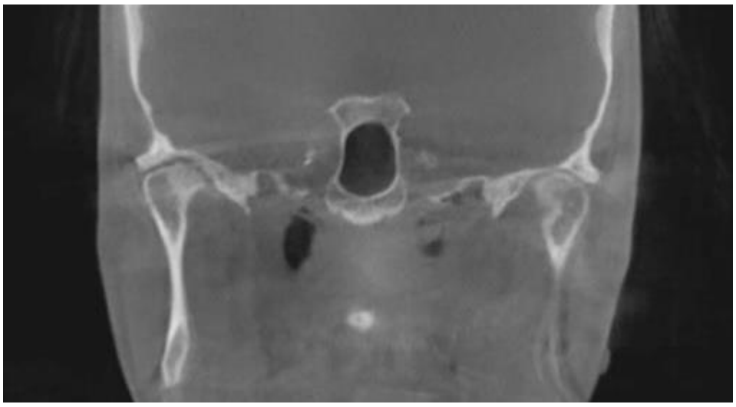


Figure 17. Osteoarthrosis of the left condyle at 2 years postoperatively using cone-beam computed tomography.

5.4.10 Patient 10 (seronegative spondylarthritis)

A 50-year-old male patient diagnosed with seronegative spondylarthritis, underwent LF I osteotomy to correct Class III malocclusion with an overbite (Figure 18). The patient had a history of restricted mouth opening and left-sided lower jaw pain for the past one and a half years. Magnetic resonance imaging (MRI) revealed an adherent disc on the left side. Despite conservative measures, including physiotherapy, lower jaw relaxation, arthroscopy, and arthrocentesis, there was no improvement in symptoms. At 3 months postoperatively, the patient reported discomfort due to hypoesthesia on the right side of the upper lip. Despite treatment with a Vitamin B-complex supplement for six months, the hypoesthesia did not improve within the first year. Osteosynthesis plates were removed secondary to pain at one and a half years after surgery. The patient still experiences hypoesthesia at the 2-year follow-up. However, both occlusal and skeletal outcomes were satisfactory.

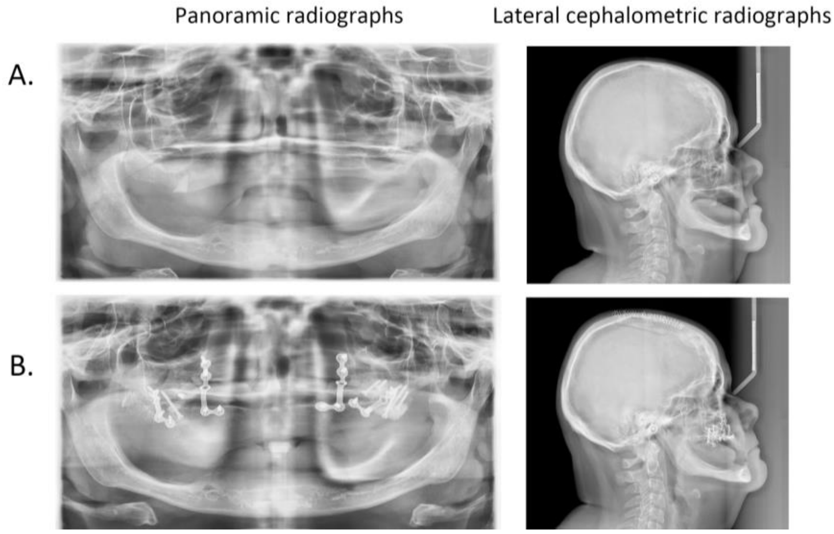


Figure 18. Panoramic and lateral cephalometric imaging. A. preoperative. B. Three months postoperative.

5.4.11 Patient 11 (pemphigus vulgaris)

A 17-year-old female patient diagnosed with pemphigus vulgaris underwent bimaxillary osteotomy for the correction of Class II malocclusion with vertical maxillary excess. The patient had experienced an episode of pemphigus vulgaris three months before the surgery. The surgical procedure proceeded smoothly. Initially, the patient had difficulty closing her mouth completely due to swelling, but this issue was resolved by the first postoperative week, and bilateral occlusal contacts were optimally established. Azathioprine treatment was started 3 months after surgery as part of the management of the underlying autoimmune pathology. No other abnormalities were detected at follow-up (Figure 19). Both occlusal and skeletal outcomes were satisfactory.

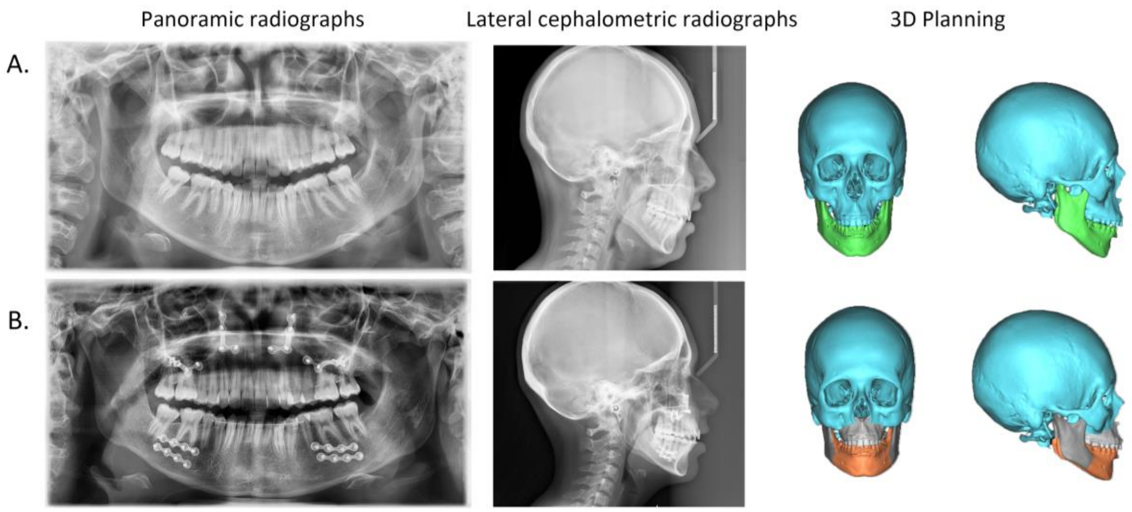


Figure 19. Panoramic and lateral cephalometric imaging with three-dimensional (3D) virtual modeling. A. Preoperative radiographs and virtual model. B. Two-year postoperative radiographs and 3D virtual plan.

5.4.12 patient 12 (Henoch-Schoenlein vasculitis)

A 23-year-old male patient diagnosed with Henoch-Schoenlein vasculitis underwent bimaxillary osteotomy for the correction of Class II malocclusion with open bite. Patient also had a history of mild hypertension. At 1-year postoperative follow-up visit, patient reported nasal obstruction and dissatisfaction with the aesthetic outcome. Consequently, the decision was made to remove the osteosynthesis material from the maxillary region and perform a reoperation. The reoperation included advancement genioplasty, nasal septum correction, and alar cinching (Figure 20). At 2 years follow-up, patient developed a fistula with pus discharge at the mandibular anterior vestibular region. Osteosynthesis material of genioplasty was removed and postoperative antibiotics (Augmentin 850 mg 3x/day) were prescribed. Both skeletal and occlusal outcomes remained stable without any further complications (Figure 21).

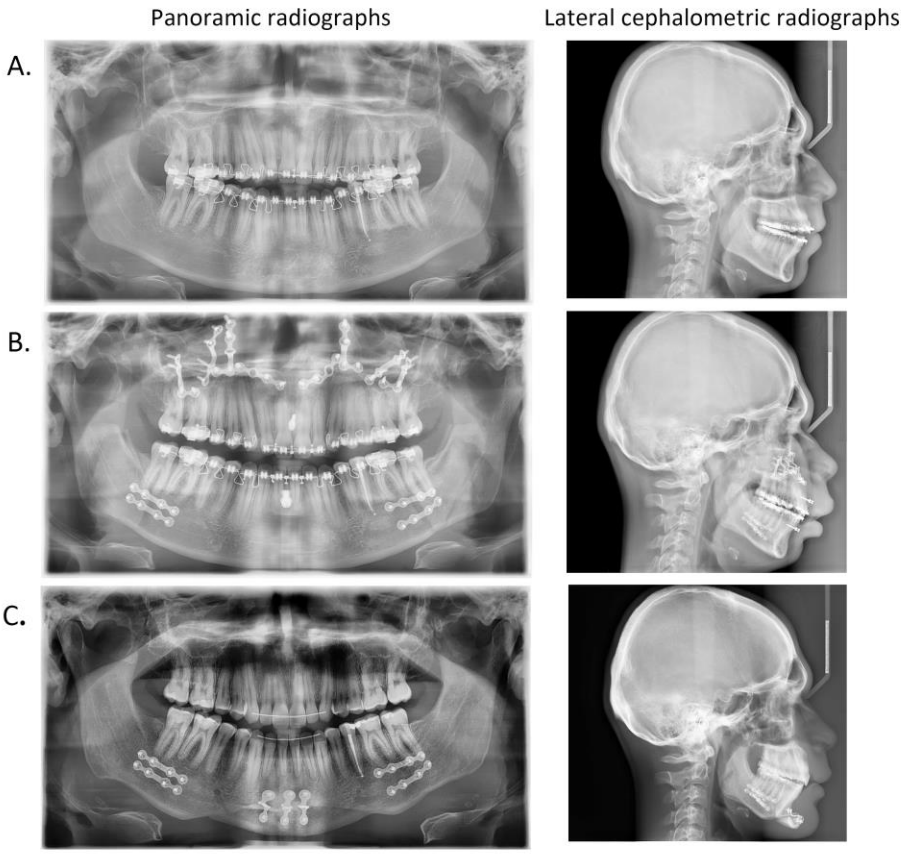


Figure 20. Panoramic and lateral cephalometric imaging. A. Preoperative. B. One-month postoperative. C. Two-year postoperative.

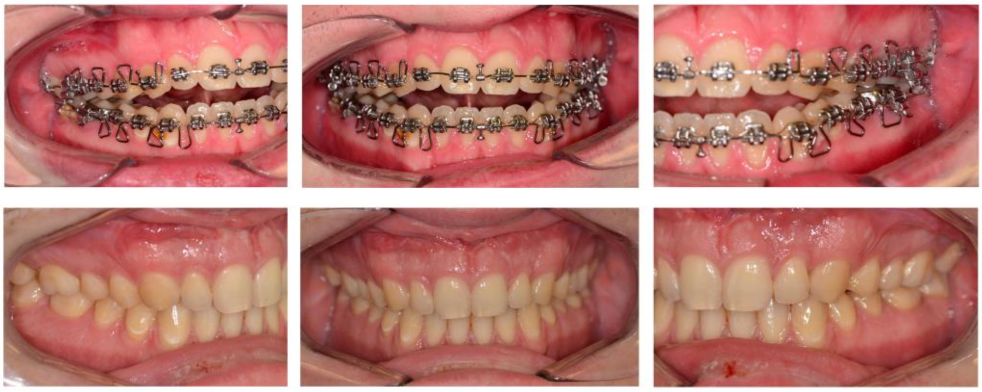


Figure 21. Intraoral photographs. A. Preoperative. B. Two-year postoperative

Table 1. Baseline characteristics of orthognathic surgical patients with autoimmune diseases

Patient	Gender	Age	BMI	autoimmune diseases	Type of Malocclusion	Orthognathic surgery	Blood loss (ml)	Operation time (h)	ASA	Outcome After orthognathic surgery
Patient 1	M	16	23.2	celiac disease	Class II	BSSO advancement	30	1	1	TMJ complication
Patient 2	F	36	22.1	Lupus	Class II	Bimax	40	3	2	Neurosensory disturbance, TMJ complication
Patient 3	F	25	21.2	Juvenile idiopathic arthritis	Class II	Bimax+ genioplasty	/	/	2	Infection, Neurosensory disturbance
Patient 4	F	51	17.7	Rheumatoid arthritis	Class II	Bimax + genioplasty	20	3	3	Infection
Patient 5	F	30	32.4	Multiple Sclerosis	Class III	Bimax	300	1	2	Infection
Patient 6	M	30	25.7	Diabetes mellitus type 1	Class II	Bimax + genioplasty	300	3	2	Neurosensory disturbance
Patient 7	F	19	24.3	scleroderma	Class II	BSSO advancement	20	0.75	2	Neurosensory disturbance
Patient 8	M	27	21.1	Psoriasis	Class III	Bimax	30	2	1	Excellent
Patient 9	F	40	19.7	Ankylosing spondylitis	Class II	BSSO advancement	150	1.5	3	Infection
Patient 10	F	50	33.6	Seronegative spondylarthritis	Class III	Le fort I	100	2	2	Neurosensory disturbance
Patient 11	F	17	20.3	Pemphigus Vulgaris	Class II	Bimax	50	2	2	Excellent
Patient 12	M	23	22.8	Henoch-Schoenlein vasculitis	Class II	Bimax	100	0.75	2	Infection

Abbreviations: BMI, Body mass index; ASA, American Society of Anesthesiologists classification; Bimax, Le Fort I osteotomy and bilateral sagittal split osteotomy; Le fort I: Le fort I osteotomy; BSSO, bilateral sagittal split osteotomy; TMJ, temporomandibular joint.

5.5 Discussion

This following case series aimed to present the outcomes and complications of orthognathic surgery in patients with autoimmune diseases. In total, 12 patients with different autoimmune diseases were included whose surgical outcomes and complications were discussed.

In the case series, 5 patients (41%) suffered from postoperative surgical site infection. Generally, the infection rate in healthy patients undergoing orthognathic surgery ranges between 3% to 21.6%, depending on different patient- and surgery-related risk factors [12–15]. In contrast, the cases in present study with autoimmune diseases had a higher risk of infection. The immune response and risk of infection might vary depending on the type of autoimmune disease and medications administered to treat the disorder [12,13,15]. In the presented cases, immunosuppressant therapy adjustment was performed at the perioperative period, nevertheless, two of five patients still suffered from postoperative infection. Hence, it is important to evaluate the patient preoperatively properly. In addition, reduced surgical trauma, antibiotic prophylaxis and nutritional support should be considered for optimizing the immune response [12]. As the mechanisms of actions of different autoimmune diseases vary, it is important to consider all possible factors that could help in modifying the immune response. Among the infection sites, the risk of mandibular infection was higher compared to maxilla. A combination of immune-suppression with certain other risk factors such as poor blood supply and gravitational pooling of saliva and debris have been hypothesized to cause higher infection in mandibular region [16–18]. Another reasoning could be the shear forces through mastication at the mandibular osteotomy sites which might produce micromovements with percolation and further facilitate infection. On the other hand, the combination of gravity and distribution of compression forces perpendicular to the osteotomy plane due to occlusal loading might cause lower infection in maxillary region [16–18]. Out of the five patients with postoperative infection, three developed infections one month after the surgery, while two experienced infections after 20 months. In a prior study, Chow et al., reported in a 15-year follow-up study related to the prevalence of complications following orthognathic surgery that the clinical onset and presentation of postoperative infections ranged between 3 days to 5 years [19]. Patients with autoimmune diseases should be followed up for an extended duration due to their heightened risk of infection. This prolonged monitoring enables the early management of infections, reducing the necessity for osteosynthesis material removal. The patients in present study were treated by removing the osteosynthesis material and antibiotics coverage. In medically healthy patients, treatment with antibiotics alone or in combination with incision and drainage is usually sufficient, without the need for the removal of plates and screws [13, 15, 16]. However, in the cases included in this study, the patients had delayed and severe infections that required the removal of fixation materials.

Concerning neurosensory disturbances, the recovery period depends on several factors, including the type of surgery, inflammation, the amount and direction of bony movement, soft tissue compression, age, the nature of the injury, and medical status [20–22]. In the present study, 5 patients (33.1%) experienced delayed recovery, a rate consistent with that in the general population [10,23]. Previous studies have recommended oral administration of adenosine triphosphate/vitamin B12 in cases of hypoesthesia, which has shown significant improvements [21]. It is worth noting that the cases presented in our study demonstrated gradual improvement over time following the removal of osteosynthesis material, which was associated with inflammation.

Regarding TMJ complications, two patients had preexisting TMJ pain and restricted mouth opening, which improved following orthognathic surgery, possibly due to changes in the condyle-disc relationship and muscular readjustment [24]. Additionally, CBCT imaging of patients with SLE and Ehler-Danlos syndrome showed early signs of condylar osteoarthrosis two years following the operation. The outcomes related to TMJ are relatively unpredictable; some patients may experience symptom improvement postoperatively, while others may develop abnormalities not present before surgery.

The main strength of the case series was the reporting of complications related to patients with different autoimmune diseases who underwent orthognathic surgery, which has yet to be thoroughly investigated. Since data on patients with autoimmune diseases were scarce, it is essential to conduct multi-center studies to draw more robust conclusions and establish guidelines for patients with different autoimmune diseases. Furthermore, future studies could compare clinical and radiological outcomes and complications of patients with autoimmune diseases versus medically fit patients to devise better management strategies.

5.6 Conclusion

The case series demonstrates that the patients with autoimmune diseases were at a high risk of infection with longer onset and neurosensory disturbances. Furthermore, the majority of patients required the removal of osteosynthesis material for treating infection and improving neurosensory feedback. A scarcity of evidence exists related to the occurrence and management of complications of patients with various autoimmune diseases and the presented findings could act as a reference for a better understanding of the diseases and devising disease-specific strategies in an attempt to reduce the complication rate in such patients.

5.7 References

[1] A. SA, Theresa LM, O. MH. Autoimmune Diseases: The Failure of Self Tolerance. Science (80-) 1990;248:1380–8. https://doi.org/10.1126/science.1972595.

[2] Angum F, Khan T, Kaler J, Siddiqui L, Hussain A. The Prevalence of Autoimmune Disorders in Women: A Narrative Review. Cureus 2020;12. https://doi.org/10.7759/cureus.8094.

[3] Rosenblum MD, Remedios KA, Abbas AK. Mechanisms of human autoimmunity. J Clin Invest 2015;125:2228–33. https://doi.org/10.1172/JCI78088.

[4] Akkara Veetil BM, Bongartz T. Perioperative care for patients with rheumatic diseases. Nat Rev Rheumatol 2012;8:32–41. https://doi.org/10.1038/nrrheum.2011.171.

[5] Peters MJ, van der Horst-Bruinsma IE, Dijkmans BA, Nurmohamed MT. Cardiovascular risk profile of patients with spondylarthropathies, particularly ankylosing spondylitis and psoriatic arthritis. Semin. Arthritis Rheum., vol. 34, Elsevier; 2004, p. 585–92.

[6] Meune C, Touzé E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology 2009;48:1309–13.

[7] Bezinover D, Iskandarani K, Chinchilli V, McQuillan P, Saner F, Kadry Z, et al. Autoimmune conditions are associated with perioperative thrombotic complications in liver transplant recipients: A UNOS database analysis. BMC Anesthesiol 2016;16:26. https://doi.org/10.1186/s12871-016-0192-3.

[8] Politis C, Jacobs R, De Laat A, De Grauwe A. TMJ surgery following orthognathic surgery: A case series. Oral Maxillofac Surg Cases 2018;4:39–52. https://doi.org/https://doi.org/10.1016/j.omsc.2018.02.003.

[9] Shujaat S, Shaheen E, Politis C, Jacobs R. Three-dimensional evaluation of long-term skeletal relapse following Le Fort I maxillary advancement surgery: a 2-year follow-up study. Int J Oral Maxillofac Surg 2022;51:501–8. https://doi.org/10.1016/j.ijom.2021.07.006.

[10] Li J, Shujaat S, Ver Berne J, Shaheen E, Couke W, Politis C, et al. Postoperative complications following orthognathic surgery in patients with rheumatic diseases: A 2-year follow-up study. Oral Dis 2022;n/a. https://doi.org/https://doi.org/10.1111/odi.14417.

[11] Agbaje JO, Casteele E Van de, Salem AS, Anumendem D, Shaheen E, Sun Y, et al. Assessment of occlusion with the T-Scan system in patients undergoing orthognathic surgery. Sci Rep 2017;7:5356. https://doi.org/10.1038/s41598-017-05788-x.

[12] Esposito S. Immune System and Surgical Site Infection. J Chemother 2001;13:12–6. https://doi.org/10.1179/joc.2001.13.Supplement-2.12.

[13] Bouchard C, Lalancette M. Infections after sagittal split osteotomy: a retrospective analysis of 336 patients. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 2015;73:158–61. https://doi.org/10.1016/j.joms.2014.07.032.

[14] Robl MT, Farrell BB, Tucker MR. Complications in Orthognathic Surgery: A Report of 1000 Cases. Oral Maxillofac Surg Clin North Am 2014;26:599–609. https://doi.org/https://doi.org/10.1016/j.coms.2014.08.008.

[15] Cousin A-S, Bouletreau P, Giai J, Ibrahim B, Louvrier A, Sigaux N. Severity and long-term complications of surgical site infections after orthognathic surgery: a retrospective study. Sci Rep 2020;10:12015. https://doi.org/10.1038/s41598-020-68968-2.

[16] Van Camp P, Verstraete L, Van Loon B, Scheerlinck J, Nout E. Antibiotics in orthognathic surgery: a retrospective analysis and identification of risk factors for postoperative infection. Int J Oral Maxillofac Surg 2021;50:643–8. https://doi.org/https://doi.org/10.1016/j.ijom.2020.09.024.

[17] Posnick JC, Choi E, Chavda A. Surgical Site Infections Following Bimaxillary Orthognathic, Osseous Genioplasty, and Intranasal Surgery: A Retrospective Cohort Study. J Oral Maxillofac Surg 2017;75:584–95. https://doi.org/10.1016/j.joms.2016.09.018.

[18] Danda AK, Ravi P. Effectiveness of postoperative antibiotics in orthognathic surgery: a meta-analysis. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 2011;69:2650–6. https://doi.org/10.1016/j.joms.2011.02.060.

[19] Chow LK, Singh B, Chiu WK, Samman N. Prevalence of Postoperative Complications After Orthognathic Surgery: A 15-Year Review. J Oral Maxillofac Surg 2007;65:984–92. https://doi.org/10.1016/j.joms.2006.07.006.

[20] Dinu C, Manea A, Tomoiagă D, Băciuț M, Almășan O, Mitre AO, et al. Recovery following Orthognathic Surgery Procedures&mdash: A Pilot Study. Int J Environ Res Public Health 2022;19. https://doi.org/10.3390/ijerph192316028.

[21] Lee C-H, Lee B-S, Choi B-J, Lee J-W, Ohe J-Y, Yoo H-Y, et al. Recovery of inferior alveolar nerve injury after bilateral sagittal split ramus osteotomy (BSSRO): a retrospective study. Maxillofac Plast Reconstr Surg 2016;38:25. https://doi.org/10.1186/s40902-016-0068-y.

[22] da Costa Senior O, Gemels B, Van der Cruyssen F, Agbaje JO, De Temmerman G, Shaheen E, et al. Long-term neurosensory disturbances after modified sagittal split osteotomy. Br J Oral Maxillofac Surg 2020;58:986–91. https://doi.org/https://doi.org/10.1016/j.bjoms.2020.05.010.

[23] Jędrzejewski M, Smektała T, Sporniak-Tutak K, Olszewski R. Preoperative, intraoperative, and postoperative complications in orthognathic surgery: a systematic review. Clin Oral Investig 2015;19:969–77. https://doi.org/10.1007/s00784-015-1452-1.

[24] Kain NJ, Lam D, Chegini H. Does mean body temperature matter in the amount of intraoperative blood loss during bimaxillary orthognathic surgery? J Oral Maxillofac Surg 2013;71:e67. https://doi.org/10.1016/j.joms.2013.06.121.

General Discussion

Conclusions & Future Perspectives

6.1 Discussion

Orthognathic surgery combined with orthodontic treatment is widely regarded as the most effective method for correcting dento-maxillofacial abnormalities by repositioning the upper jaw, lower jaw, and/or chin [1]. Although this procedure offers significant functional and aesthetic improvement, it is crucial to be aware of potential complications that may arise during the recovery period. These complications can vary in severity and may require additional treatment or management [2]. The existing body of evidence related to postoperative outcomes following orthognathic surgery predominantly stems from studies conducted on healthy populations, without accounting for the impact of systemic comorbidities. Nonetheless, there is an increasing number of patients with systemic diseases requiring orthognathic surgical treatment [3]. Through an analysis of relevant literature, we observed that patients with specific systemic diseases are associated with distinct postoperative complications. For instance, individuals with rheumatic diseases exhibit a higher risk of reoperation, primarily due to residual retrognathic profiles or open bite conditions. Furthermore, patients with osteopenia, who are prone to mandible backward clockwise skeletal relapse, present lower levels of serum Estradiol (E2), which could contribute to condylar region resorption owing to the impediment of the condyle's natural reparative capacity when confronted with local inflammatory factors [4,5]. Thirdly, patients with myotonic dystrophy and congenital myopathy face an increased risk of respiratory complications due to weakness in the respiratory muscles. This could result in extended postoperative intubation or the need for urgent reintubation. Furthermore, facial muscle weakness in these patients could contribute to delayed wound healing [6]. While other systemic diseases may also impact orthognathic surgery outcomes, the limited evidence with inadequate sample sizes hinder our ability to draw conclusive findings.

The overall aim of this Ph.D. project was to gain a comprehensive understanding of the impact and recovery of patients with systemic diseases following orthognathic surgery. These insights and findings have the potential to develop treatment strategies. The general hypothesis posits that patients with systemic diseases are more likely to experience postoperative complications compared to healthy patients undergoing orthognathic surgery.

This doctoral thesis presents a progressive study that delves into the effects of systemic diseases on orthognathic surgery outcomes, starting with a fundamental question: What is the prevalence of systemic diseases among the entire population undergoing orthognathic surgery? **Article 1** of this thesis investigated the data and found that approximately 10 percent of patients undergoing this surgical intervention exhibited the presence of at least one form of systemic disease. Among these diseases, inflammatory joint disorders, endocrinological disorders, and syndromes were the most prevalent. The present study revealed a noticeable difference in the age at which surgical intervention was undertaken among patients afflicted with syndromes as opposed to those diagnosed with endocrinological, gastrointestinal, or inflammatory joint disorders. Patients with syndromes typically commence treatment at a younger age, utilizing techniques such as distraction osteogenesis or orthodontics, and prioritizing the correction of any remaining malocclusion after facial skeleton maturation [7]. The ability to address maxillary hypoplasia surgically at a younger age contributes to the lower average age in this group. In contrast, it is observed that individuals with endocrinological disorders manifest a confluence of midface hypoplasia and mandibular hyperplasia, leading to an extended duration before surgical intervention is pursued, consequently leading to an increased average age at surgical procedures. Patients who suffer from inflammatory joint disorders typically have to wait longer for surgery because they first need to manage and control the inflammation in their joints. Additionally, syndromes, malignancies, and endocrinological disorders are all associated with Class III malocclusion. Syndromes, caused by genetic mutations affecting facial skeleton growth, often result in Class II or Class III malocclusion. However, the specific development of Class II or III malocclusion varies among syndromes due to the involvement of multiple genetic pathways [8]. Malignancies could cause deformities due to tumor location, local radiotherapy, or systemic chemotherapy, thereby impacting the growth of the affected skeleton. Regarding endocrinological disorders, fundamental research has established a link between the fibroblast growth factor (FGF) pathway, influenced by thyroid hormones, and alterations in bone metabolism [9]. The identification of gain-of-function mutations within the FGF3 gene has been established in individuals diagnosed with Muenke syndrome and achondroplasia, two distinct medical conditions that share the common feature of Class III malocclusion [10]. Conversely, the manifestation of Class II malocclusion has been linked to the presence of loss-of-function mutations within the FGF1 and FGF2 genes [11]. A study by Kamal et al. [12] revealed that children diagnosed with hypothyroidism exhibit specific dental characteristics, including enamel hypoplasia, postponed eruption of teeth, and anterior open bite.

Based on the data collected in Article 1, we proceeded to design a 20-year single-center prevalence study, presented in **Article 2**, which revealed that nearly one in six orthognathic surgery patients suffered from systemic conditions. Asthma, hypertension, attention deficit and hyperactivity disorder, and hypothyroidism were identified as the most prevalent systemic conditions. When comparing the findings of these two prevalence studies within this thesis to other studies [3], notable differences were observed in the lists of the most prevalent systemic conditions. These disparities could be attributed to variations in study design and the characteristics of the patient population. In article 2, we conducted a comprehensive comparison between groups with and without systemic conditions, considering factors such as gender, age, blood loss, surgery duration, and malocclusions. The group with systemic diseases exhibited a higher average age and weight at surgery, both of which are known factors associated with increased risk of wound infection, longer operating periods, and increased blood loss [13].

Given the prevalence and features of systemic diseases in the patients who underwent orthognathic surgery, our objective was to investigate the impact of these conditions on orthognathic surgery outcomes. In order to analyze postoperative complications and identify potential risk factors, a retrospective cohort study was conducted, specifically focusing on patients with rheumatic diseases. The inclusion of patients with rheumatic diseases was deliberate due to their significant representation among individuals with systemic diseases, as demonstrated in Article 1. Furthermore, existing studies have provided evidence suggesting a possible association between rheumatic diseases and an increased risk of reoperation and infection. In **Article 3**, after adjusting for confounding variables such as age, gender, type of orthognathic surgery, intraoperative blood loss, duration of operation, antirheumatic medication, and bone grafting, our findings indicated an increased risk of infection following orthognathic surgery in patients with rheumatic diseases, which is consistent with the evidence from hip and knee orthopedic surgical procedures [14,15]. Several studies have indicated that rheumatoid arthritis patients have a higher susceptibility to infection than the healthy population as a result of immunological alterations caused by the disease itself [16]. The altered immune response in rheumatic patients impairs wound healing and compromises defense mechanisms against bacteria. Moreover, the chronic inflammation associated with rheumatic diseases further weakens the immune system, creating a favorable environment for bacterial growth and colonization. For patients with rheumatic diseases undergoing orthognathic surgery, the following recommendations are suggested: conduct a comprehensive preoperative evaluation to optimize disease control and medication management, ensuring minimal risk of postoperative infection; facilitating multidisciplinary collaboration among healthcare professionals for tailoring preoperative planning, perioperative management, and postoperative care according to individual patient needs; comprehensive infection prevention measures should be followed, encompassing oral hygiene instructions, appropriate antibiotic usage, stringent sterile techniques, and diligent wound care practices; patients should receive education regarding the heightened risk of infection, with a particular emphasis on the significance of maintaining good oral hygiene, adhering to medication management, and attending regular follow-up appointments for care and monitoring.

Regarding the risk of surgical relapse, our study found that it was relatively low and not significantly associated with rheumatic diseases, which is consistent with previous studies [17,18]. However, certain studies have reported higher relapse rates (21% to 48%) after BSSO (mandibular advancement) in patients with juvenile idiopathic arthritis and resorptive TMDs [19,20]. Despite the lack of significant correlation between rheumatic diseases and postoperative TMJ pain in our study, it is recognized that patients suffering from rheumatic conditions might experience pain in the joint. According to a matched case-control study, patients with rheumatic diseases have significantly more severe clinical and radiological TMJ symptoms [21]. In addition, rheumatic patients with preexisting TMJ dysfunction who undergo orthognathic surgery, particularly in cases of mandibular advancement, face an increased risk of experiencing a notable exacerbation of TMJ symptoms following the procedure [22].

Viviana et al. highlighted the association between asthma and dentofacial anomalies, specifically noting a higher prevalence of dental crossbite, overbite, and overjet among asthmatic individuals [23]. Similarly, Kumar et al. discovered high prevalence rates of anterior open bite and posterior crossbite in asthma patients aged between 6 and 12 years old [24]. Furthermore, previous studies have emphasized that asthmatic patients are more likely to develop pulmonary problems after the procedure compared to healthy populations [25]. Considering these findings, **Article 4** of this thesis presents a retrospective cohort study aimed at comparing postoperative outcomes between patients with and without asthma. In this study, we examined the occurrence of postoperative complications in asthmatic patients and found that they had an increased incidence of open bite relapse compared to their healthy counterparts. Specifically, the maxilla was found to be relative stability, while the mandible tended to experience setback relapse. The increased risk of open bite relapse in asthmatic patients might be attributed to the prevalent phenomenon of increased mouth breathing within this population [26,27]. One study reported a significant correlation between asthma and mouth breathing in adults, with an adjusted odds ratio (OR) of 5.21, suggesting that this breathing pattern persists even after resolving the underlying anatomical or functional issue [28]. Neural adaptations, alterations in central upper airway control, muscle function, and skeletal changes have been proposed as potential explanations for this phenomenon [29]. Notably, the consequences of mouth breathing during childhood and adolescence could persist into adulthood [30]. Our findings align with Wriedt et al. [31], who observed a strong correlation between persistent mouth breathing following orthognathic surgery and open bite relapse, with an OR of 12.5. They emphasized the importance of providing functional treatment, including speech therapy and correcting dysfunctional parameters during swallowing and breathing to address this issue. Mouth breathing disrupts the natural dynamics within the oral cavity, leading to tangible consequences such as altered tongue posture, abnormal swallowing patterns, increased vertical forces exerted on the teeth and jaws, and muscular imbalances in the orofacial region. These factors collectively contribute to a lowered tongue posture, which fails to provide adequate support for the upper dental arch. When the volume of the tongue relatively increases within the oral cavity, the mandibular position might relapse following mandibular setback surgery [32]. Moreover, the muscles responsible for opening the mouth exert backward pressure on the mandible, causing it to shift distally and potentially affecting the positioning and alignment of teeth [33]. Therefore, it is recommended that asthmatic patients undergoing orthognathic surgery alter their breathing patterns and avoid postoperative relapse by participating in myofunctional therapy. Furthermore, it is crucial to optimize asthma management and achieve good control prior to surgery. Patients should be educated about the influence of asthma on orthognathic surgery outcomes and the significance of maintaining optimal asthma control throughout the surgical and recovery phases. Regular monitoring of asthma control and adjustment of medication as needed, should be emphasized as part of the comprehensive treatment approach. Another potential contributing factor to open bite relapse in asthmatic patients could be root resorption resulting from prolonged administration of medications such as steroids [34]. An increase in external apical root resorption has been reported in the asthma group following orthodontic treatment, according to Scott et al. [35]. In article 4, a significant association between asthma and temporomandibular disorders was not found, which is consistent with previous research [36]. However, other studies have indicated that asthmatic patients are more likely to suffer from TMDs, possibly due to a shared immune response that releases similar proinflammatory cytokines in both conditions [37,38]. Although asthmatic patients did not experience any postoperative respiratory complications in our study, they remain at a higher risk of pulmonary complications during the postoperative period [25,38]. It is important to note that the conflicting findings might be attributed to the limited sample size of asthmatic patients in our study, and caution should be exercised when interpreting the results.

Due to the limited number of available patients, we conducted a case-series study focusing on orthognathic surgery complications in patients with autoimmune diseases. **Article 5** demonstrated that patients with autoimmune diseases were at a high risk of developing neurosensory disturbances and infection with longer onset. In most cases, the removal of osteosynthesis material was necessary to address infection and improve neurosensory feedback. Previous studies have suggested the potential effectiveness of orally administering adenosine triphosphate/vitamin B12 in treating hypoesthesia [40]. The increased risk of infection in individuals with autoimmune diseases undergoing surgical procedures might be attributed to a combination of factors, including compromised immune function, chronic inflammation, immunosuppressive medications, and inflammatory response triggered by surgery. Persistent activation of the immune system and the release of pro-inflammatory molecules could disrupt normal tissue healing processes and impair the body's ability to fight off infection [41,42]. Therefore, a thorough preoperative patient evaluation is crucial. Preventive measures such as minimizing surgical trauma, administering antibiotic prophylaxis, and providing nutritional support should be considered to optimize the immune response [41]. Additionally, long-term follow-up is essential for patients with autoimmune diseases who are at a higher risk of infection, as it enables early management without the need for the removal of osteosynthesis material.

6.2 Conclusions

This thesis explored the relationship between systemic diseases and orthognathic surgery outcomes through a series of comprehensive studies. **Articles 1** and **2** revealed a significant prevalence of systemic diseases among orthognathic surgery patients, providing a foundational understanding of this specific patient population. In **Article 3**, we conducted a rigorous analysis that highlighted an elevated risk of postoperative infection among patients with rheumatic diseases, even after accounting for factors such as age, gender, and operation time. **Article 4** focused on asthmatic patients, uncovering a higher occurrence of open bite relapse compared to their healthy counterparts. Remarkably, while the maxilla displayed relative stability, the mandible tended to relapse in these patients. Finally, **Article 5** delved into patients with autoimmune diseases, revealing an increased vulnerability to infection with a delayed onset and the presence of neurosensory disturbances. Notably, a significant number of these patients required the removal of osteosynthesis material to address infection and improve neurosensory feedback.

Collectively, these findings emphasize the importance of considering systemic diseases in orthognathic surgery patient care. This underlines the requirement for personalized preoperative assessments, careful postoperative monitoring, and establishing specific management strategies to lessen the risks linked with systemic diseases. This work contributes to the growing body of knowledge in the field and provides valuable insights for optimizing the care and outcomes of orthognathic surgery patients with systemic diseases.

6.3 Future perspectives

- To gain further insights into the relationship between systemic diseases and malocclusion, it is necessary to expand our data to also encompass individuals with mild malocclusion who undergo orthodontic treatment without orthognathic surgery.

- Most of the existing research on systemic diseases and orthognathic surgery is retrospective. Future studies need to focus on well-designed, controlled prospective multicenter studies with larger sample sizes. Such studies will allow researchers to gather robust data and draw definitive conclusions regarding the management and outcomes of patients with systemic diseases.
- Furthermore, it would be valuable to compare clinical and radiological outcomes as well as complications in patients with systemic diseases versus medically fit patients in an attempt to devise better management strategies.
- Although certain systemic conditions are associated more frequently with specific malocclusions, the exact role of systemic diseases in the development of malocclusion remains unclear. Further research is necessary to delve into the underlying mechanisms and establish a clear understanding of the relationship between systemic diseases and malocclusion.
- While studies have investigated postoperative infection in patients with rheumatic diseases, the understanding of how these diseases cause infection remains incomplete. Future research should aim to unravel the intricate relationship between rheumatic diseases and postoperative infection to enhance patient care and outcomes. Additionally, CBCT-based studies should be conducted to objectively determine TMJ changes in patients with rheumatoid arthritis following orthognathic surgery.
- The relationship between asthma and open bite relapse poses a significant concern that has yet to receive sufficient attention. To gain a better understanding of this relationship and assess the safety and effectiveness of potential preventive measures, it is recommended to conduct further prospective case-control studies. These studies should aim to evaluate three-dimensional changes in skeletal structure, root development, and airway morphology.
- It is essential to develop standardized protocols for risk assessment and preoperative optimization in patients with systemic diseases. Future research should explore variations in presurgical orthodontic treatment, surgical planning, and procedures, in an attempt to create treatment strategies that are tailored specifically to the disease of each patient.

6.4 References

[1] Naran S, Steinbacher DM, Taylor JA. Current Concepts in Orthognathic Surgery. Plast Reconstr Surg 2018;141:925e-936e. https://doi.org/10.1097/PRS.0000000000004438.

[2] Jedrzejewski M, Smektala T, Sporniak-Tutak K, Olszewski R. Preoperative, intraoperative, and postoperative complications in orthognathic surgery: a systematic review. Clin Oral

Investig 2015;19:969–77. https://doi.org/10.1007/s00784-015-1452-1.

[3] Venugoplan SR, Nanda V, Turkistani K, Desai S, Allareddy V. Discharge patterns of orthognathic surgeries in the United States. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 2012;70:e77-86. https://doi.org/10.1016/j.joms.2011.09.030.

[4] Yang HJ, Hwang SJ. Bone mineral density and mandibular advancement as contributing factors for postoperative relapse after orthognathic surgery in patients with preoperative idiopathic condylar resorption: A prospective study with preliminary 1-year follow-up. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;120:112–8. https://doi.org/10.1016/j.oooo.2015.03.004.

[5] Karayianni K, Horner K, Mitsea A, Berkas L, Mastoris M, Jacobs R, et al. Accuracy in osteoporosis diagnosis of a combination of mandibular cortical width measurement on dental panoramic radiographs and a clinical risk index (OSIRIS): The OSTEODENT project. Bone 2007;40:223–9. https://doi.org/10.1016/j.bone.2006.07.025.

[6] Bezak BJ, Arce KA, Jacob A, Van Ess J. Orthognathic Surgery in Patients with Congenital Myopathies and Congenital Muscular Dystrophies: Case Series and Review of the Literature. J Oral Maxillofac Surg 2016;74:601–9. https://doi.org/10.1016/j.joms.2015.07.023.

[7] Derderian James CS. Syndromic Craniosynostosis. Semin Plast Surg 2012;26:64–75. https://doi.org/10.1055/s-0032-1320064.

[8] Bartzela TN, Carels C, Maltha JC. Update on 13 syndromes affecting craniofacial and dental structures. Front Physiol 2017;8:1038. https://doi.org/10.3389/fphys.2017.01038.

[9] Leitch VD, Bassett JHD, Williams GR. Role of thyroid hormones in craniofacial development. Nat Rev Endocrinol 2020;16:147–64. https://doi.org/10.1038/s41574-019-0304-5.

[10] Lee YC, Song IW, Pai YJ, Chen S De, Chen YT. Knock-in human FGFR3 achondroplasia mutation as a mouse model for human skeletal dysplasia. Sci Rep 2017;7. https://doi.org/10.1038/srep43220.

[11] Jarzabek K, Wolczynski S, Lesniewicz R, Plessis G, Kottler M.L. Evidence that FGFR1 loss-of-function mutations may cause variable skeletal malformations in patients with Kallmann syndrome. Adv Med Sci 2012;57:314–21. https://doi.org/10.2478/v10039-012-0036-4.

[12] Kamal AT, Mahmood HT, Fida M. The Implications of Endocrinology in Orthodontics–Literature Review. Balk J Dent Med 2020;24:8–13.

[13] Tjeertes EKM, Hoeks SE, Beks SBJ, Valentijn TM, Hoofwijk AGM, Stolker RJ. Obesity--a risk factor for postoperative complications in general surgery? BMC Anesthesiol 2015;15:112. https://doi.org/10.1186/s12871-015-0096-7.

[14] Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population - based study. Arthritis Rheum 2002;46:2287–93.

[15] Bongartz T, Halligan CS, Osmon DR, Reinalda MS, Bamlet WR, Crowson CS, et al. Incidence and risk factors of prosthetic joint infection after total hip or knee replacement in patients with

rheumatoid arthritis. Arthritis Care Res (Hoboken) 2008;59:1713–20. https://doi.org/https://doi.org/10.1002/art.24060.

[16] Baker JF, George MD. Prevention of Infection in the Perioperative Setting in Patients with Rheumatic Disease Treated with Immunosuppression. Curr Rheumatol Rep 2019;21:17. https://doi.org/10.1007/s11926-019-0812-2.

[17] Pagnoni M, Amodeo G, Fadda MT, Brauner E, Guarino G, Virciglio P, et al. Juvenile idiopathic/rheumatoid arthritis and orthognathic surgery without mandibular osteotomies in the remittent phase. J Craniofac Surg 2013;24:1940–5.

[18] Thaller SR, Cavina C, Kawamoto HK. Treatment of orthognathic problems related to scleroderma. Ann Plast Surg 1990;24:528—533. https://doi.org/10.1097/00000637-199006000-00010.

[19] Stoor P, Hodzic Z, Arte S. Surgical Treatment of Dentofacial Deformities Caused by Juvenile Idiopathic Arthritis. J Craniofac Surg 2018;29:e51–7.

[20] Oye F, Bjornland T, Store G. Mandibular osteotomies in patients with juvenile rheumatoid arthritic disease. Scand J Rheumatol 2003;32:168–73.

[21] Helenius LMJ, Hallikainen D, Helenius I, Meurman JH, Könönen M, Leirisalo-Repo M, et al. Clinical and radiographic findings of the temporomandibular joint in patients with various rheumatic diseases. A case-control study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:455–63. https://doi.org/https://doi.org/10.1016/j.tripleo.2004.06.079.

[22] Wolford LM, Reiche-Fischel O, Mehra P. Changes in temporomandibular joint dysfunction after orthognathic surgery. J Oral Maxillofac Surg 2003;61:655–60; discussion 661. https://doi.org/10.1053/joms.2003.50131.

[23] Faria VCM, de Oliveira MA, Santos LA, Santoro IL, Fernandes ALG. The Effects of Asthma on Dental and Facial Deformities. J Asthma 2006;43:307–9.

[24] Kumar SS, Nandlal B. Effects of asthma and inhalation corticosteroids on the dental arch morphology in children. J Indian Soc Pedod Prev Dent 2012;30:242–9.

[25] Lin C-S, Chang C-C, Yeh C-C, Chung C-L, Chen T-L, Liao C-C. Postoperative Adverse Outcomes in Patients With Asthma: A Nationwide Population-based Cohort Study. Medicine (Baltimore) 2016;95:e2548–e2548. https://doi.org/10.1097/MD.0000000000002548.

[26] Izuhara Y, Matsumoto H, Nagasaki T, Kanemitsu Y, Murase K, Ito I, et al. Mouth breathing, another risk factor for asthma: the Nagahama Study. Allergy 2016;71:1031–6. https://doi.org/https://doi.org/10.1111/all.12885.

[277] Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. J Allergy Clin Immunol 2000;106:S201-5.

[28] Gomes-Filho IS, Soledade-Marques KR, Seixas da Cruz S, de Santana Passos-Soares J, Trindade SC, Souza-Machado A, et al. Does periodontal infection have an effect on severe asthma in adults? J Periodontol 2014;85:e179-87. https://doi.org/10.1902/jop.2013.130509.

[29] Corrêa ECR, Bérzin F. Mouth Breathing Syndrome: Cervical muscles recruitment during nasal

inspiration before and after respiratory and postural exercises on Swiss Ball. Int J Pediatr Otorhinolaryngol 2008;72:1335–43. https://doi.org/https://doi.org/10.1016/j.ijporl.2008.05.012.

[30] Trevisan ME, Boufleur J, Soares JC, Haygert CJP, Ries LGK, Corrêa ECR. Diaphragmatic amplitude and accessory inspiratory muscle activity in nasal and mouth-breathing adults: A cross-sectional study. J Electromyogr Kinesiol 2015;25:463–8.

[31] Wriedt S, Buhl V, Al-Nawas B, Wehrbein H. Combined Treatment of Open Bite – Long-term Evaluation and Relapse Factors. J Orofac Orthop / Fortschritte Der Kieferorthopädie 2009;70:318–26. https://doi.org/10.1007/s00056-009-9912-3.

[32] Togawa R, Iino S, Miyawaki S. Skeletal Class III and open bite treated with bilateral sagittal split osteotomy and molar intrusion using titanium screws. Angle Orthod 2010;80:1176–84.

[33] Grippaudo C, Paolantonio EG, Antonini G, Saulle R, La Torre G, Deli R. Association between oral habits, mouth breathing and malocclusion. Acta Otorhinolaryngol Ital Organo Uff Della Soc Ital Di Otorinolaringol e Chir Cerv-Facc 2016;36:386–94. https://doi.org/10.14639/0392-100X-770.

[34] Krishnan V, Davidovitch Z. Integrated clinical orthodontics. John Wiley & Sons; 2012.

[35] McNab S, Battistutta D, Taverne A, Symons AL. External apical root resorption of posterior teeth in asthmatics after orthodontic treatment. Am J Orthod Dentofac Orthop 1999;116:545–51. https://doi.org/https://doi.org/10.1016/S0889-5406(99)70187-3.

[36] Nishioka M, Ioi H, Matsumoto R, Goto TK, Nakata S, Nakasima A, et al. TMJ osteoarthritis/osteoarthrosis and immune system factors in a Japanese sample. Angle Orthod 2008;78:793–8.

[37] Fredricson AS, Khodabandehlou F, Weiner CK, Naimi-Akbar A, Adami J, Rosén A. Are there early signs that predict development of temporomandibular joint disease? J Oral Sci 2018;60:194–200. https://doi.org/10.2334/josnusd.17-0073.

[38] Song H-S, Shin J-S, Lee J, Lee YJ, Kim M, Cho J-H, et al. Association between temporomandibular disorders, chronic diseases, and ophthalmologic and otolaryngologic disorders in Korean adults: A cross-sectional study. PLoS One 2018;13:e0191336.

[39] Warner DO, Warner MA, Barnes RD, Offord KP, Schroeder DR, Gray DT, et al. Perioperative respiratory complications in patients with asthma. Anesthesiology 1996;85:460–7. https://doi.org/10.1097/00000542-199609000-00003.

[40] Lee C-H, Lee B-S, Choi B-J, Lee J-W, Ohe J-Y, Yoo H-Y, et al. Recovery of inferior alveolar nerve injury after bilateral sagittal split ramus osteotomy (BSSRO): a retrospective study. Maxillofac Plast Reconstr Surg 2016;38:25. https://doi.org/10.1186/s40902-016-0068-y.

[41] Esposito S. Immune System and Surgical Site Infection. J Chemother 2001;13:12–6. https://doi.org/10.1179/joc.2001.13.Supplement-2.12.

[42] Bouchard C, Lalancette M. Infections after sagittal split osteotomy: a retrospective analysis of 336 patients. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 2015;73:158–61. https://doi.org/10.1016/j.joms.2014.07.032.

Summary

Orthognathic surgery represents the preferred approach for correcting dento-maxillofacial deformities by repositioning the maxilla, mandible, and/or chin. While this procedure offers both functional and aesthetic improvements, it is crucial to consider potential complications that might arise during the recovery period, as their severity could vary and necessitate additional treatment. Through a comprehensive analysis of relevant literature, it has been observed that patients with specific systemic diseases are prone to distinct postoperative complications. For instance, due to residual retrognathic profiles or exposed bite conditions, rheumatic disease patients are at an increased risk for reoperation. Additionally, patients with osteopenia exhibit an inclination towards mandible backward clockwise skeletal relapse. Thirdly, patients with myotonic dystrophy and congenital myopathy face an increased risk of respiratory complications and experience delayed recovery. Although other systemic diseases might also impact the outcomes of orthognathic surgery, the limited research evidence and inadequate sample sizes currently impede our ability to draw conclusive findings.

The aim of this Ph.D. project was to gain a comprehensive understanding of the impact and recovery of patients with systemic diseases following orthognathic surgery, with the goal of improving treatment strategies. The hypothesis posits that patients with systemic diseases are at a higher risk of experiencing postoperative complications compared to healthy patients.

This doctoral thesis presents a progressive study that delves into the effects of systemic diseases on orthognathic surgery, beginning with a fundamental question: What is the prevalence of systemic diseases among the entire population undergoing orthognathic surgery? To address this question, a prevalence study was conducted as described in **Article 1** of this thesis, revealing that approximately one in 10 patients undergoing orthognathic surgery had a systemic condition. Among these conditions, inflammatory joint disorders, endocrinological disorders, and syndromes were the most prevalent. Furthermore, variations in the age at the time of surgery were observed between patients with syndromes and those with endocrinological, gastrointestinal, and inflammatory joint disorders. Additionally, syndromes, malignancies, and endocrinological disorders were all found to be associated with Class III malocclusion.

Building upon the data collected in Article 1, a subsequent 20-year single-center prevalence study was conducted at another hospital to explore this topic further. **Article 2** presents the findings of this study, which revealed that approximately 1 in 6 patients had a systemic condition in the orthognathic

population. Asthma, hypertension, attention deficit and hyperactivity disorder, and hypothyroidism were identified as the most prevalent systemic conditions. A comparison was made between the patients with systemic diseases and those without it, considering factors such as gender, age, blood loss, surgery duration, and malocclusions. The group with systemic diseases exhibited a higher average age at surgery as well as the average weight, both known risk factors associated with increased chances of wound infection, longer operating periods, and increased blood loss.

Considering the prevalence and features of systemic diseases in patients who underwent orthognathic surgery, our objective was to assess the impact of these conditions on orthognathic surgery outcomes. To achieve this, we conducted a retrospective cohort study with the aim of analyzing postoperative complications in individuals with rheumatic diseases and identifying potential risk factors. In **Article 3**, we found that patients with rheumatic diseases were at a higher risk of contracting a postoperative infection. Our study did not establish a strong association between rheumatic diseases and surgical relapse or postoperative TMJ pain, which is consistent with previous research. However, it is important to acknowledge that other studies have reported a higher incidence of relapse and TMJ symptoms in rheumatic patients.

Asthma, a chronic respiratory disorder, often coexists with dentoskeletal deformities in patients undergoing orthognathic surgery. Therefore, in **Article 4**, we conducted a retrospective cohort study to compare postoperative outcomes between patients with asthma and a healthy control group. Our findings revealed that asthmatic patients exhibited a higher incidence of open bite relapse compared to their healthy counterparts. Furthermore, while the maxilla exhibited relative stability, the mandible tended to experience setbacks.

Due to the limited number of available patients, we conducted a case-series study focusing on individuals with autoimmune diseases. In **Article 5**, We demonstrated that patients with autoimmune diseases are susceptible to postoperative infections with a prolonged onset and neurosensory disturbances. Furthermore, most of these patients needed to have osteosynthesis material removed for the sake of infection therapy and enhanced neurosensory feedback.

The findings of this doctoral thesis highlight the prevalence of systemic diseases in orthognathic populations and identify specific complications associated with rheumatic diseases, osteopenia, myotonic dystrophy, congenital myopathy, asthma, and autoimmune diseases.

Samenvatting

Orthognatische chirurgie vertegenwoordigt de voorkeursbenadering voor het corrigeren van dento-maxillofaciale afwijkingen door het herpositioneren van de bovenkaak, onderkaak en/of kin. Hoewel deze procedure zowel functionele als esthetische verbeteringen biedt, is het cruciaal om mogelijke complicaties die zich tijdens de herstelperiode kunnen voordoen, in overweging te nemen, aangezien de ernst ervan kan variëren en aanvullende behandeling vereist kan zijn. Uit een uitgebreide analyse van relevante literatuur is gebleken dat patiënten met specifieke systemische ziekten vatbaar zijn voor onderscheidende postoperatieve complicaties. Zo hebben individuen met reumatische aandoeningen een verhoogd risico op heroperatie, voornamelijk als gevolg van resterende retrognatische profielen of open beet condities. Bovendien vertonen patiënten met osteopenie een neiging tot achterwaartse kloksgewijze skeletale terugval van de onderkaak. Ten derde lopen patiënten met myotone dystrofie en congenitale myopathie een verhoogd risico op ademhalingscomplicaties en ervaren zij vertraagd herstel. Hoewel andere systemische ziekten ook invloed kunnen hebben op de resultaten van orthognatische chirurgie, belemmeren het beperkte onderzoeksbewijs en ontoereikende steekproefgroottes momenteel onze mogelijkheid om definitieve bevindingen te trekken.

Het doel van dit promotieproject is om een uitgebreid inzicht te krijgen in de impact en het herstel van patiënten met systemische ziekten na orthognatische chirurgie, met als doel de behandelingstrategieën te verbeteren. De hypothese stelt dat patiënten met systemische ziekten een hoger risico lopen op postoperatieve complicaties in vergelijking met gezonde patiënten.

Deze doctoraatscriptie presenteert een vooruitstrevende studie die dieper ingaat op de effecten van systemische ziekten op orthognatische chirurgie, beginnend met een fundamentele vraag: Wat is de prevalentie van systemische ziekten bij de gehele populatie die een orthognatische ingreep ondergaat? Om deze vraag te beantwoorden, werd een prevalentiestudie uitgevoerd zoals beschreven in **Artikel 1** van deze scriptie, waaruit bleek dat ongeveer één op de tien patiënten die een orthognatische ingreep ondergingen een systemische aandoening had. Onder deze aandoeningen waren inflammatoire gewrichtsaandoeningen, endocrinologische aandoeningen en syndromen het meest voorkomend. Bovendien werden variaties in de leeftijd op het moment van de operatie waargenomen tussen patiënten met syndromen en patiënten met endocrinologische, gastro-intestinale en inflammatoire gewrichtsaandoeningen. Bovendien bleken syndromen, maligniteiten en endocrinologische aandoeningen allemaal geassocieerd te zijn met klasse III malocclusie.

Voortbouwend op de verzamelde gegevens in Artikel 1 werd een daaropvolgende 20-jarige prevalentiestudie uitgevoerd in een ander ziekenhuis om dit onderwerp verder te verkennen. **Artikel 2** presenteert de bevindingen van deze studie, waaruit bleek dat ongeveer één op de zes patiënten die een orthognatische ingreep ondergingen een systemische aandoening had. De meest voorkomende systemische aandoeningen die werden geïdentificeerd waren astma, hypertensie, aandachtsstoornis met hyperactiviteit en hypothyreoïdie. Er werd een vergelijking gemaakt tussen de groepen met en zonder systemische aandoeningen, waarbij factoren als geslacht, leeftijd, bloedverlies, operatieduur en malocclusies in overweging werden genomen. De groep met systemische aandoeningen vertoonde een hogere gemiddelde leeftijd op het moment van de operatie en een groter gewicht, beide bekende risicofactoren die verband houden met een verhoogde kans op wondinfectie, groter bloedverlies en langere operatietijden.

Gezien de prevalentie en kenmerken van systemische ziekten in de orthognatische populatie, was ons doel om de impact van deze aandoeningen op de resultaten van orthognatische chirurgie te onderzoeken. Om dit te bereiken, hebben we een retrospectieve cohortstudie uitgevoerd met als doel postoperatieve complicaties te analyseren bij patiënten met reumatische aandoeningen en potentiële risicofactoren te identificeren. In **Artikel 3** is onze bevinding dat patiënten met reumatische aandoeningen een verhoogd risico op postoperatieve infectie hebben, in lijn met het bewijs gebaseerd op orthopedische chirurgische ingrepen aan heupen en knieën. Onze studie heeft geen sterk verband aangetoond tussen reumatische aandoeningen en chirurgisch terugval of postoperatieve TMJ-pijn, wat in lijn is met eerdere onderzoeken. Het is echter belangrijk op te merken dat andere studies een hogere incidentie van terugval en TMJ-symptomen hebben gerapporteerd bij patiënten met reumatische aandoeningen.

Astma, een chronische respiratoire aandoening, komt vaak voor in combinatie met dentoskeletale afwijkingen bij patiënten die een orthognatische chirurgie ondergaan. Daarom hebben we in **Artikel 4** een retrospectieve cohortstudie uitgevoerd om de postoperatieve resultaten te vergelijken tussen patiënten met astma en een gezonde controlegroep. Onze bevindingen toonden aan dat astmatische patiënten een hogere incidentie van terugval van een open beet vertoonden in vergelijking met hun gezonde tegenhangers. Bovendien vertoonde de maxilla relatieve stabiliteit, terwijl de mandibula neigde tot achteruitgang.

Vanwege het beperkte aantal beschikbare patiënten hebben we een casestudie uitgevoerd die zich richtte op individuen met auto-immuunziekten. In **Artikel 5** hebben we aangetoond dat patiënten met auto-immuunziekten een hoog risico lopen op infecties met een langere aanvang en neurosensorische stoornissen ervaren. Bovendien moest een meerderheid van deze patiënten het osteosynthesemateriaal verwijderen voor de behandeling van infecties en verbetering van neurosensorische feedback.

De bevindingen van dit proefschrift benadrukken de prevalentie van systemische ziekten in orthognatische populaties en identificeren specifieke complicaties die geassocieerd worden met reumatische aandoeningen, osteopenie, myotone dystrofie, congenitale myopathie, astma en auto-immuunziekten.

Scientific Acknowledgements

The author of this thesis was supported by the China Scholarship Council (CSC). Without the dedication of other participants, I would not be able to finish this job, and for that, I would want to express my gratitude.

Article 1-2: Thanks to the efforts of **Dr. Sohaib Shujaat** and **Dr. Jonas Ver Berne** for their valuable contributions.

Article 3-5: I would like to thank **Dr. Sohaib Shujaat** for his help with language revision and his expert advice. The completion of these projects would not have been possible without his expertise.

Lastly, I extend my sincere appreciation to my Promoter **Prof. Dr. Reinhilde Jacobs**, as well as my **co-promoters Prof. Dr. Constantinus Politis** and **Dr. Eman Shaheen**, for their scientific assistance and contributions throughout the process of my doctoral studies.

Personal Contribution

The projects and main conceptual ideas were developed by Jiqing Li, the author of this thesis. Additionally, Jiqing Li collected clinical and radiological data from patients, conducted experiments, analyzed the data, and took the lead in writing the peer-reviewed manuscripts. The scientific guidance and support from Prof. Dr. Reinhilde Jacobs, the thesis promoter, and other co-authors were also instrumental in the research process. The specific contributions of Jiqing Li to each article are outlined as follows:

Article 1 (second author): Conceptualization, methodology, formal analysis, investigation, and writing of the review and editing process.

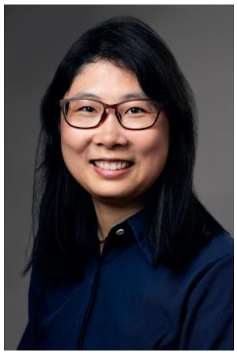
Article 2 (fourth author): Conceptualization, methodology, and writing of the review and editing.

Article 3-5 (first author): Conceptualization, methodology, validation, formal analysis, investigation, data curation, writing of the original draft, writing of the review, and editing, visualization, and project administration.

Conflict of Interest

Regarding the publishing of this study, the authors state that they have no conflicts of interest.

Curriculum Vitae **JIQING LI**



Phone: +32485038306 E-mail: jiqingli.g@gmail.com; 1183687154@qq.com

Personal Details

Date and place of birth: 15 April 1991, Xuzhou, China

Nationality: Chinese.

Education

09/2018—present Doctoral researcher at OMFS-IMPATH research group, KU Leuven, Belgium

Promoter: Prof. Dr. Reinhilde Jacobs

Co-promoter: Prof. Dr. Constantinus Politis and Dr. ir. Eman Shaheen

09/2014—06/2017 Department of oral and maxillofacial surgery, West China School of Stomatology Sichuan University, China

Master of Dental Medicine in Oral and Maxillofacial Surgery

Promoter: Prof. Dr. Jihua Li

09/2010—07/2011 Exchange student for one year, Faculty of Dentistry, West China School of Stomatology Sichuan University, China

09/2009—06/2014 Faculty of Dentistry, Shandong University, China

Bachelor of Dental Medicine

Experience

09/ 2013—07/2018 Clinical postgraduate and trainee of resident doctor in Oral and Maxillofacial Surgery department at West China Hospital of Stomatology Sichuan University

09/2013—06/2014 Trainee at Shandong Provincial Hospital

Certificates and awards

Qualification and practicing certificates for dentists in China

Certificate of standardized training for residents in China

Third prize in Chinese traditional literature writing (2010) at Shandong University

Exchange Student Scholarship (2011) at Shandong University

Excellent Academic Scholarship (2015-2017) at Sichuan University

International Presentation

[Oral presentation] Jiqing Li, Evaluation of postoperative outcomes in orthognathic surgery patients with systemic diseases. Presented at the Bone-Bond Colloquium at Academic Center for Dentistry Amsterdam (ACTA), Amsterdam, Netherlands, 7 July 2022.

[E-poster] Jiqing Li, A patient-specific approach for orthognathic surgery to prevent complications in asthmatic subject. Presented at the International Oral Health Symposium 2022 on Innovation, Strategy, and Future Perspectives, online symposium hosted by Karolinska Institutet, 7-8 June 2022.

Publications related to the thesis

J. Li, J. Ver Berne, S. Shujaat, E. Shaheen, C. Politis, R. Jacobs. Influence of systemic comorbidities on the outcome of orthognathic surgery: A scoping review. Journal of Stomatology, Oral and Maxillofacial Surgery.123 (6), e956-e961(2022). https://doi.org/10.1016/j.jormas.2022.06.018.

J. Ver Berne, **J. Li,** E. Shaheen, C. Politis, H. Peeters, R. Jacobs. Prevalence and characteristics of systemic conditions in patients undergoing orthognathic surgery: a retrospective study. International Journal of Oral and Maxillofacial Surgery. 51 (9), 1205-1210 (2022). https://doi.org/10.1016/j.ijom.2022.02.004

J. Ver Berne, C. Politis, J. Meyns, **J. Li**, R. Jacobs. Prevalence of systemic conditions in an orthognathic surgery population: a 20-year single-center study, Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, 134(2), 163-167 (2022). https://doi.org/10.1016/j.oooo.2022.01.003.

J. Li, S. Shujaat, J. Ver Berne, E. Shaheen, Wim Coucke, C. Politis, R. Jacobs. Post-operative complications following orthognathic surgery in patients with rheumatic diseases: A 2-year follow-up study. Oral diseases. (2022) Epub ahead of print. https://doi.org/10.1111/odi.14417

J. Li, S. Shujaat, E. Shaheen, J. Ver Berne, C. Politis, R. Jacobs. Postoperative complications in asthmatic patients following orthognathic surgery: A two-year follow-up study. Journal of Stomatology, Oral and Maxillofacial Surgery, 124(3), 101388. (2023). https://doi.org/10.1016/j.jormas.2023.101388

J. Li, S. Shujaat, E. Shaheen, C. Politis, R. Jacobs. Autoimmune diseases and orthognathic surgery: a case series of 12 patients. Journal of Plastic, Reconstructive & Aesthetic Surgery. 84: 413-421 (2023). https://doi.org/10.1016/j.bjps.2023.06.017

Other Publications

J. Li, Y. Xu, Yu Wang, Y. Hsu, P. Wang, J. LI. The Treatment of Hyaluronidase for the Skin Necrosis Caused by Hyaluronic Acid Injection-Induced Embolism: A Rabbit Auricular Model Study. Aesthetic Plastic Surgery. 43, 1362–1370 (2019). https://doi.org/10.1007/s00266-019-01398-2.

MQ. Wang, LL. Lan, T. Li, **JQ. Li,** YF. Li. The effect of oxytocin on osseointegration of titanium implant in ovariectomized rats. CONNECT TISSUE RES. 2016 May; 57(3): 220-5.