



Long-Term Skeletal Relapse Following Mandibular Advancement With Bilateral Sagittal Split Osteotomy

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**LONG-TERM SKELETAL RELAPSE FOLLOWING MANDIBULAR
ADVANCEMENT WITH BILATERAL SAGITTAL SPLIT OSTEOTOMY**

By

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I have reviewed this thesis. It represents work done by the author under my guidance/supervision.

Primary Mentor: Dr. Meredith August

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OVERVIEW

Class II malocclusion is a common dentofacial deformity characterized by mandibular hypoplasia, leading to functional, aesthetic and psychological compromise. Bilateral sagittal split osteotomy is the most frequently performed surgical procedure for mandibular advancement in the treatment of mandibular hypoplasia. One major concern of bilateral sagittal split osteotomy is the postoperative relapse, which is difficult to predict, prevent, and treat because of its multifactorial etiology. Understanding the risk factors for relapse is critical to effective prediction and prevention. Independent risk factors for long-term relapse, as well as the associations among risk factors and relapse, remain to be elucidated.

In our first study, we performed univariate and multivariate linear regression analyses of 9 independent variables commonly cited in the literature as being associated with relapse and assessed long-term (≥ 2 years) skeletal relapse as the dependent variable. We found that preoperative mandibular plane angle, the magnitude of mandibular advancement, and counterclockwise mandibular rotation were independent risk factors for long-term skeletal relapse. Therefore, patients with higher mandibular plane angles who underwent larger advancement with counterclockwise mandibular rotation were predisposed to more long-term skeletal relapse.

In our second study, we performed stratification analyses and interaction analyses to detect if there was a significant interaction between these predictors and to demonstrate how the interaction influenced the associations between covariates and relapse. We identified significant interactions of gender*mandibular rotation and mandibular plane angle*mandibular

rotation for horizontal long-term skeletal relapse, concluding that females or patients with a mandibular plane angle $\geq 30^\circ$, who underwent counterclockwise mandibular rotation were predisposed to greater horizontal long-term skeletal relapse compared to those who underwent clockwise mandibular rotation.

The results of these 2 studies have collectively improved our understanding of the risk factors and their effects on long-term skeletal relapse. Although relapse cannot be avoided entirely, understanding this information will optimize treatment planning and long-term stability in high-risk patients. Based on our findings, we recommend judicious use of counterclockwise mandibular rotation to minimize the risk of relapse, especially in females and patients with high mandibular plane angles.

PAPER 1

Independent Risk Factors for Long-term Skeletal Relapse After Mandibular

Advancement with Bilateral Sagittal Split Osteotomy

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Abstract

The purpose of this retrospective cohort study is to identify the independent risk factors for long-term skeletal relapse following mandibular advancement with bilateral sagittal split osteotomy. Univariate and multivariate linear regression analyses were performed including 9 common risk factors for relapse as independent variables and horizontal/vertical long-term (≥ 2 years) skeletal relapse as the dependent variable, respectively. Ninety-six patients including 66(68.8%) females, with an average age of 29.7 ± 10.5 years, were analyzed. We found 1.6 ± 1 mm horizontal and 0.9 ± 0.7 mm vertical long-term skeletal relapse over an average follow-up of 3.8 ± 1.8 years after initial mandibular advancement of 8.8 ± 2.4 mm. Multivariate analyses identified age, preoperative mandibular plane angle, bimaxillary surgery, counterclockwise mandibular rotation, and the magnitude of mandibular advancement to be significantly associated with horizontal long-term skeletal relapse. Preoperative mandibular plane angle, counterclockwise mandibular rotation, and the magnitude of mandibular advancement were significantly associated with vertical long-term skeletal relapse. Our results showed that preoperative mandibular plane angle, the magnitude of mandibular advancement, and counterclockwise mandibular rotation of the mandible were independent risk factors for both horizontal and vertical long-term skeletal relapse. Although long-term skeletal relapse cannot be avoided entirely, understanding the independent risk factors and their contributions will optimize treatment planning and long-term stability.

Introduction

Class II malocclusion is a common dentofacial deformity characterized by mandibular hypoplasia and retrognathia, leading to functional, aesthetic and psychological compromise. Treatment often requires a combination of orthodontic and orthognathic surgery. Mandibular advancement with bilateral sagittal split osteotomy is the most frequently performed orthognathic procedure to correct mandibular retrognathia. Nonetheless, one major concern of bilateral sagittal split osteotomy is the postoperative relapse which can be categorized as 1) short- or long-term relapse based on the timing of occurrence, 2) skeletal or dental relapse based on the anatomic landmarks, and 3) horizontal or vertical relapse based on the direction. Short-term relapse often happens within 6 months postoperatively due to osteotomy site slippage and condylar sag. It can be minimized by adequate intraoperative condylar positioning and rigid internal fixation. Dental relapse can also be compensated with postoperative orthodontic treatment if the skeletal component is insignificant. However, the long-term skeletal relapse, which may continue to occur several years postoperatively, is difficult to predict, prevent, and treat because of its multifactorial etiology.

Understanding the putative risk factors is critical to effectively predict and prevent relapse. Previous studies have sought to identify several potential risk factors for relapse after bilateral sagittal split osteotomy, including age, gender, body mass index, bone mineral density, preoperative mandibular plane angle, preoperative temporomandibular joint pathology, single or double jaw surgery, direction of mandibular rotation, magnitude of mandibular advancement,

use of bone graft, genioplasty, type and material of fixation, postoperative maxillomandibular fixation, and orthodontic treatment¹⁻⁷. These factors may influence the healing stability of the osteotomy, increase soft tissue tension and lead to subsequent condylar remodeling/resorption, considered a major cause of long-term relapse. However, independent risk factors for long-term skeletal relapse remain to be elucidated due to distinct patient populations, strict patient eligibility, small sample sizes, different definitions and measurements of cephalometric parameters, limited follow-up periods, and inappropriate statistical methods in the literature.

The purpose of this study is to answer the following research question: Among patients who underwent mandibular advancement with bilateral sagittal split osteotomy, what are the independent risk factors for long-term skeletal relapse? The investigators hypothesize that there exists a set of independent risk factors for long-term relapse. The specific aim of this study is to identify these independent risk factors for horizontal and vertical relapse through multivariate analyses of long-term follow-up data.

Materials and Methods

Study Design and Sample

To address the research purpose, the investigators designed a retrospective cohort study. The study population was composed of all patients who underwent mandibular advancement with bilateral sagittal split osteotomy for the management of mandibular retrognathia or obstructive sleep apnea in the Department of Oral and Maxillofacial Surgery at Massachusetts General Hospital between June 1, 2005, to June 1, 2017. Patients were identified through the

institutional patient data registry. Study approval was obtained from the Partners Institutional Review Board (Protocol number 2017P002223).

Inclusion criteria were: complete medical and radiographic records including preoperative (T0), within 1 week postoperative (T1), and a minimum of 2 years postoperative (T2) lateral cephalograms. Patients were excluded as study subjects if they had: 1) wire osteosynthesis fixation; 2) congenital or craniofacial syndromes, including cleft lip/palate; 3) a history of facial tumor or facial fracture; 4) previous temporomandibular joint or orthognathic surgery (excepting palatal expansion); 5) severe jaw asymmetry which required significant mandibular rotation; 6) incomplete medical records or less than 2 years follow-up.

Study Variables

Predictor variables included 1) demographic variables: gender, age; 2) anatomic variables: preoperative temporomandibular joint symptom, mandibular plane angle; 3) surgical variables: single or double jaw surgery, the direction of mandibular rotation, the magnitude of mandibular advancement, concomitant genioplasty, and the type of fixation. The temporomandibular joint symptom was defined as one or more of the following: locking, crepitus, click, arthralgia, disc displacement, and dislocation, and limited movement of the mandible. Mandibular plane angle was defined as the angle between the Sella-Nasion line and the mandibular plane (Gonion-Gnathion line). The direction of mandibular rotation included clockwise rotation or counterclockwise rotation of the mandible. The magnitude of MA was measured intraoperatively and verified by measuring on the T1 cephalograms. Concomitant genioplasty

was defined as either genial tubercle advancement or conventional genioplasty. The type of fixation included miniplates+monocortical screws, bicortical screws or a combination of both.

The primary outcome variable was the horizontal long-term skeletal relapse, which was defined as a horizontal change of the B-point on T2 versus T1 lateral cephalograms. The secondary outcome variable was the vertical long-term skeletal relapse, which was defined as a vertical change of the B-point on T2 versus T1 lateral cephalograms. We defined the change as a relapse if the B-point moved in the opposite direction to the initial surgery. Otherwise, it was coded as 0.

Data Collection

All lateral cephalograms were taken in the Department of Oral and Maxillofacial Surgery at Massachusetts General Hospital using standard settings and protocols that ensured consistency. The cephalometric landmarks used in the present study include B-point, Sella, and Nasion. The x - y coordinates were established as follows: The x -axis was a line through Sella and 7° downward from the Sella-Nasion line. The y -axis was a line perpendicular to the x -axis and through Sella ([Figure 1](#)). The distance from B to the x -axis and B to the y -axis was measured at T0, T1, and T2. Cephalometric analysis was performed using Dolphin Imaging Software 11.8 (Dolphin Imaging and Management Solutions, Chatsworth, CA) by two authors (Y.C and J.Z). All measurements and calculations were performed by Y.C. 1 month apart and by J.Z. independently to ensure intra-observer and inter-observer reliabilities.

Data Analyses

Intra- and inter-observer reliabilities were assessed using the intra-class correlation coefficient. An intra-class correlation coefficient > 0.75 was considered excellent reliability. Continuous variables (age, mandibular plane angle, mandibular advancement, horizontal and vertical long-term skeletal relapse) were expressed as mean $\pm$ standard deviation, or median and range if they were not normally distributed. Categorical variable (fixation method) or binary variables (gender, +/- temporomandibular joint symptom, single or bimaxillary surgery, clockwise rotation or counterclockwise rotation, +/- genioplasty) were reported as proportion or percentage. Univariate and multivariate linear regression analyses were performed using all predictor variables as independent variables, and horizontal and vertical long-term skeletal relapse as the dependent variable, respectively. The predictor variable was forced into the final model even if the univariate analysis showed statistical insignificance because all 9 predictors have been previously shown to be clinically related to relapse in the literature. The results were presented as coefficients with corresponding 95% confidence intervals and associated p-values. A p-value < 0.05 was considered statistically significant. Statistical analysis was done using STATA v15.0 (StataCorp LLC, College Station, Texas, USA). This study is reported according to the STROBE guidelines.

Results

Study Sample

A total of 315 patients who underwent bilateral sagittal split osteotomy advancement were initially screened. Of these, 96 patients met the inclusion and exclusion criteria. Most exclusions were secondary to inadequate long-term follow-up. The flow diagram for sample selection is illustrated in [Figure 2](#). All cephalometric measurements were highly correlated (intra-class correlation coefficient=0.95 for intra-observer correlation and inter-class correlation coefficient=0.91 for inter-observer correlation). There were 66(68.8%) females and 30(31.2%) males with an average age of 29.7 ± 10.5 years. Sixty (62.5%) patients reported a temporomandibular joint symptom. The average mandibular plane angle was $33.1 \pm 5.7^\circ$. Seventy-three (76%) patients underwent double jaw surgery. In 60 patients (62.5%), the mandible was advanced with a counterclockwise rotation. The average mandibular advancement was 8.8 ± 2.4 mm. Sixty-seven patients (69.8%) underwent concurrent genioplasty. Bicortical fixation screws were used in 61 patients (63.5%), followed by miniplates and monocortical screws in 26 (27.1%) patients and a combination of both in 9 (9.4%) patients. We observed 1.6 ± 1 mm horizontal long-term skeletal relapse (18% of initial MA) and 0.9 ± 0.7 mm vertical long-term skeletal relapse over an average follow-up of 3.8 ± 1.8 years. Twenty-three (24%) patients displayed a ≥ 2 mm horizontal long-term skeletal relapse and 9 (9.4%) patients presented a ≥ 2 mm vertical relapse. ([Table 1](#)).

Risk Factors for Horizontal Long-term Skeletal Relapse

Univariate linear regression analyses indicated a significant correlation between horizontal long-term skeletal relapse and age, mandibular plane angle, bimaxillary surgery, counterclockwise rotation, mandibular advancement, genioplasty, and the type of fixation. After multivariate adjustment, only age (coefficient=-0.01, 95% CI: -0.02, -0.001, $p=0.036$), mandibular plane angle (coefficient=0.03, 95% CI: 0.01, 0.05, $p=0.001$), bimaxillary surgery (coefficient=0.31, 95% CI: 0.05, 0.56, $p=0.018$), counterclockwise rotation (coefficient=0.4, 95% CI: 0.22, 0.58, $p<0.001$), and mandibular advancement (coefficient=0.29, 95% CI: 0.23, 0.35, $p<0.001$) were significantly associated with horizontal long-term skeletal relapse. The R^2 was 0.75 for mandibular advancement, 0.43 for mandibular plane angle, and 0.36 for bimaxillary surgery ([Table 2](#)).

Risk Factors for Vertical Long-term Skeletal Relapse

Univariate linear regression analyses showed a significant correlation between vertical long-term skeletal relapse and mandibular plane angle, bimaxillary surgery, counterclockwise rotation, and mandibular advancement. Multivariate linear regression demonstrated that mandibular plane angle (coefficient=0.05, 95%CI: 0.02, 0.07, $p<0.001$), counterclockwise rotation (coefficient=0.34, 95% CI: 0.1, 0.58, $p=0.007$), and mandibular advancement (coefficient=0.12, 95% CI: 0.04, 0.19, $p=0.005$) were significantly associated with vertical

relapse. The R^2 was 0.31 for the mandibular plane angle, 0.27 for mandibular advancement, and 0.15 for counterclockwise rotation ([Table 3](#)).

Discussion

The long-term stability after mandibular advancement with bilateral sagittal split osteotomy has been the interest of research for decades due to its clinical significance and multifactorial etiologies. The results of the present study showed that age, mandibular plane angle, mandibular advancement, bimaxillary surgery, and counterclockwise rotation were independent risk factors for horizontal long-term skeletal relapse, whereas mandibular plane angle, mandibular advancement, and counterclockwise rotation were independent risk factors for vertical long-term skeletal relapse. Specifically, younger patients with higher mandibular plane angle, who underwent larger bimaxillary advancement with counterclockwise rotation were predisposed to more horizontal long-term skeletal relapse. Patients with low or high mandibular plane angle, who underwent larger mandibular advancement and counterclockwise rotation were prone to more vertical long-term skeletal relapse.

Age

Few studies have evaluated the postoperative stability following mandibular advancement with bilateral sagittal split osteotomy in adolescents. Younger patients were reported with a higher risk of late relapse compared to adults. Proffit et. al.⁸ compared the long-term stability of bilateral sagittal split osteotomy advancement in 32 adolescents (mean age 16 years) and 52

adults (mean age 35 years). They found that adolescent patients had a significantly greater horizontal and vertical relapse at pogonion from 1 to 5 years postoperatively. Fifty percent of adolescent patients had 2 to 4 mm horizontal relapse and another 25% had >4 mm backward movement, whereas only 15% of adult patients had 2 to 4 mm and none had >4 mm relapse. In contrast, Den Besten et al.⁹ showed that the mean horizontal relapse was 0.5 mm (11% of initial mandibular advancement) in adolescents under age 18, and 0.9 mm (16.4% of initial mandibular advancement) in patients aged 20 to 24 years after 1-year follow-up. Although the amount and proportion of relapse in this group were higher in younger patients, differences were not statistically significant.

Possible explanations of greater relapse in adolescent patients could be the active growth/remodeling of the condyle and mandible, as well as the better biomechanical stability of harder cortical bone in adults. Discordant growth between maxilla and mandible might occur after a bilateral sagittal split osteotomy in growing adolescence, leading to malocclusion and facial disharmony. In our cohort, bilateral sagittal split osteotomy was commonly performed after the adolescent growth spurt, except in cases with severe obstructive sleep apnea or sociopsychological problems warranting an earlier operation. Patients in the present study had an average age of 29.7 ± 10.5 years (14-64 years) because we included patients not only with dentofacial deformities, but also those with obstructive sleep apnea, who were generally older. Although multivariate linear regression showed a negative association between age and horizontal relapse, the coefficient of age was small, and the upper boundary of 95% confidence interval was close to 0 with a p-value close to 0.5. After we divided the cohort into adolescents

and adults based on the 18-year cutoff, we found only 8 of 96 patients were adolescent at the time of surgery. Subgroup analysis between adolescent and adult patients showed no statistical significance in any predictor or outcome variables. Therefore, no definitive conclusion can be drawn regarding any predisposition to relapse in adolescent patients.

The magnitude of Mandibular Advancement

Multiple authors have reported a significant positive correlation between the magnitude of mandibular advancement and relapse. Borstlap et al.¹⁰ identified a relationship between the amount of mandibular advancement and horizontal relapse in a multicenter prospective study consisting of 222 patients. The mean horizontal skeletal relapse at pogonion was 0.9 mm after 2 years follow-up. They found that 35(16%) patients had a clinically significant relapse (average 3.3 mm), whereas other 187 “stable” patients had a mean 0.4 mm relapse. Joss et al. reported 2.4 mm horizontal relapse (50% of initial mandibular advancement) at B point after an initial mandibular advancement of 4.8 mm in 16 patients over an average of 12.7 years follow-up after bilateral sagittal split osteotomy advancement. They concluded that the amount of mandibular advancement was correlated with long-term relapse. Similarly, Maal et al.¹¹ performed a 3D cone beam computed tomography analysis and found a positive correlation between mandibular advancement and skeletal relapse in 18 patients 1 year after bilateral sagittal split osteotomy.

In accordance with previous studies, we found a significantly positive association between the magnitude of mandibular advancement and both horizontal and vertical long-term skeletal

relapse (**Figure 3**). Based on our multivariate linear regression model, we would expect an incremental 0.29 mm of horizontal and 0.12 mm of vertical long-term skeletal relapse with each 1 mm increase of mandibular advancement, holding other variables constant. This was consistent with Tabrizi et al.¹², who predicted an increase of 0.17 mm horizontal and 0.09 mm vertical relapse for each 1 mm increase of mandibular advancement.

The magnitude of mandibular advancement appears to be the most critical contributor to relapse. Joss and Vassalli et al. ranked it the most important risk factor associated with relapse. Tabrizi et al. found that 74% of horizontal relapse and 42% of vertical relapse at B point was related to mandibular advancement. In agreement with their findings, the R^2 of MA in our study indicated that mandibular advancement was the most important contributor to horizontal long-term skeletal relapse (75%) and the second most important contributor to vertical long-term skeletal relapse (27%) following preoperative mandibular plane angle.

The inherent instability of large advancement is often attributed to the smaller cross-sectional area of bone contact between mandibular segments, the stretching and tension of the soft tissue envelope and subsequent condylar remodeling/resorption. The stretching and tension of muscles, including medial and lateral pterygoid, masseteric, digastric, suprahyoid and infrahyoid muscles, may generate biomechanical overload on the condyle head, leading to progressive condylar resorption/remodeling, which is believed as the major cause to long-term relapse following bilateral sagittal split osteotomy¹³.

Preoperative Mandibular Plane Angle

High mandibular plane angle has been described in many studies as a predisposing factor for relapse. Borstlap et al. showed that patients with a high mandibular plane angle were prone to relapse. Eggensperger et al.¹⁴ found that high angle patients had a 30% higher rate of long-term relapse. Mobarak et al.¹⁵ reported 20 patients with high mandibular plane angle ($43.0^{\circ} \pm 4.0^{\circ}$) who demonstrated both higher frequency and greater amount of horizontal relapse compared to 20 patients with low mandibular plane angle ($20.8^{\circ} \pm 4.9^{\circ}$). They found low angle patients had short-term relapse 2 months after surgery due to early osteotomy site movement. On the other hand, high angle patients were predisposed to long-term relapse which continued to occur 3 years postoperatively. Joss and Vassalli et al. concluded that patients with high mandibular plane angle had a more horizontal relapse, whereas low angle patients had a more vertical relapse. In a 3D cone beam computed tomography study, Xi et al.¹⁶ noted that high mandibular plane angle patients had less condylar volume, leading to a higher risk of condylar remodeling/resorption and subsequent skeletal relapse. Schwartz et al.¹⁷ reported a mean relapse of 1.3 mm (11% of initial mandibular advancement) after an average mandibular advancement of 11.6 mm at B-point during a 19.5 months follow-up. They noted that patients with high or low angle exhibited significantly higher amounts of skeletal relapse compared to patients with medium angle. Tabrizi et al. reported a positive correlation between the change of mandibular plane angle and vertical relapse at B point, but not horizontal relapse.

Our results indicate a significant positive association between mandibular plane angle and horizontal relapse (**Figure 4**). We would expect an incremental 0.03 mm of horizontal relapse for each degree increase of preoperative mandibular plane angle, holding other variables constant. However, an interesting finding was that the association between the mandibular plane angle and the vertical relapse was not linear, but quadric (**Figure 4**). After we divided mandibular plane angle into low(<25°), medium(between 25° and 35°), and high (>35°) groups, we found a negative association between mandibular plane angle and vertical long-term skeletal relapse in the low angle group (Coefficient=-0.24, 95% CI: -0.32, -0.17, $p<0.001$), a positive association in the high angle group (Coefficient=0.12, 95% CI: 0.08, 0.17, $p<0.001$) and no significant association in the medium angle group ($p=0.31$).

In our cohort, mandibular plane angle had considerable influences on both horizontal and vertical long-term skeletal relapse. The R^2 of mandibular plane angle in our linear regression model showed mandibular plane angle to be the most critical contributor to vertical long-term skeletal relapse (31%) and the second most critical contributor to horizontal long-term skeletal relapse after the magnitude of mandibular advancement (43%). Clinical appreciation of the role of the mandibular plane angle on relapse will lead to better preoperative discussion with patients regarding anticipated stability and the need for longitudinal follow-up.

Counterclockwise Rotation of the Mandible

The effect of counterclockwise rotation on skeletal relapse remains an area of active debate. Hwang et al.¹⁸ suggested that counterclockwise rotation might increase functional

loading of the anterior-superior surface of the condyle, making it prone to resorption and subsequent skeletal relapse. However, disagreements regarding the role of counterclockwise rotation in relapse exist in the literature. Goncalves et al.¹⁹ noted 0.1 ± 2.5 mm relapse (1% of MA) following counterclockwise rotation with 10 ± 4.4 mm MA at point B in 56 obstructive sleep apnea patients with a high mandibular plane angle of $45.9^\circ \pm 5.5^\circ$ over an average of 1.4 years follow-up. Reyneke et al.²⁰ found no significant difference in skeletal stability between clockwise rotation and counterclockwise rotation of the maxillomandibular complex in 66 patients over an average of 13.7 years follow-up. Esteves et al.²¹ reported a minor backward movement of 0.57 mm and a downward movement of 0.07 mm at B-point after counterclockwise rotation of the maxillomandibular complex in 10 patients with high mandibular plane angle.

Our study shows counterclockwise rotation to be significantly associated with both horizontal and vertical long-term skeletal relapse. Patients who underwent counterclockwise rotation were expected to have an average of 0.4 mm greater horizontal long-term skeletal relapse and 0.34 mm greater vertical long-term skeletal relapse than patients with clockwise rotation when holding other variables constant. The R^2 showed that 15% of relapse can be explained by the counterclockwise mandibular rotation.

Bimaxillary Surgery

It remains controversial whether bimaxillary surgery is associated with a higher risk or greater amount of relapse. Several authors have shown stable outcomes after bimaxillary

surgery. Emshoff et. al.²² reported a forward movement of 0.3 ± 2.0 mm and upward movement of 1.6 ± 1.2 mm at B point in 26 patients 1-year following bimaxillary surgery. Proffit et. al.²³ characterized single jaw surgery as highly stable and double jaw surgery with rigid fixation as stable within the first year postoperatively. However, from 1 to 5 years postoperatively, one-third of the patients who underwent double jaw surgery exhibited >2 mm backward movement at B-point.

Our study shows bimaxillary surgery to be significantly associated with horizontal but not vertical long-term skeletal relapse. Patients who underwent bimaxillary surgery were expected to have an average of 0.31 mm greater horizontal relapse than patients who had bilateral sagittal split osteotomy alone when holding other variables constant. The R^2 indicated that 36% of horizontal relapse could be explained by bimaxillary surgery.

Study Strength

Most of the previous stability studies have applied univariate analyses such as a comparison between 2 or more groups regardless of the heterogeneity of patient demographics, anatomical, or surgical characteristics. Although the results of univariate analyses are suggestive, caution is required when interpreting these results due to the bias introduced by unadjusted characteristics. To study a multifactorial phenomenon like relapse, multivariate analyses with adjustment of the covariates is a more suitable approach. If a risk factor is still statistically significant after multivariate adjustment, then we can define it as an independent risk factor.

Distinct from previous studies, we included a total of 9 important risk factors to be associated with long-term skeletal relapse in this multivariate analysis. To provide real-world evidence, we included all patients who had mandibular advancement with bilateral sagittal split osteotomy, thus increasing the generalizability and translation of these results to clinical practice. Although this was a single-center retrospective study, we had a relatively large sample size with long follow-up compared to existing literature.

Study Limitations

Being retrospective in design, this study had several inherent limitations. The bilateral sagittal split osteotomies were performed by multiple surgeons. Surgeons might have their preferences when performing this procedure, which introduced heterogeneity into this group. Although the follow-up duration was consistently greater than 2 years (average 3.8 years), this is still less than ideal for relapse study since relapse is thought to continue many years postoperatively.

Of the initial 315 patients who underwent mandibular advancement with BSSO, 198 patients were excluded because of inadequate follow-up data, 96 patients were finally included for analysis. We further compared the demographic and clinical characteristics between those patients who were included and excluded. We found lower percentages of patients who underwent bimaxillary and counterclockwise rotation in those excluded patients. Therefore, this inclusion criteria introduced a selection bias, which could cause an overestimate or underestimate of the associations between predictors and outcomes. We did not perform

sensitivity analysis, which would be helpful to correct selection bias. Furthermore, the majority of patients (68.8%) in this cohort were female and it is unclear what role hormonal disparity plays in condylar resorption/remodeling. Gender itself was not found to be a significant variable associated with relapse, so the effect of gender on relapse remain to be elucidated.

Many details of the clinical, surgical and orthodontic treatment were not available in the medical record. Therefore, possible contributing factors to relapse were omitted due to their absences. For example, it is well established that preexisting temporomandibular joint pathology plays a critical role in postsurgical instability²⁴. However, temporomandibular joint imaging records were not routinely available to analyze. We therefore used the temporomandibular joint symptom as an indication of pathology. However, it is noteworthy that asymptomatic joint could also demonstrate significant pathology. Furthermore, the use of postoperative intermaxillary fixation, surgical splints of varying designs and thickness, and perioperative orthodontic treatment varied considerably in this group. In addition, postoperative morphological, volumetric and positional changes of the condyles were not measured. Moreover, we did not include baseline comorbidities as predictor variables in our analyses. This is because most of the patients in our sample were young adults without significant comorbidities. Even for OSA patients, few comorbidities were found in this cohort and were unlikely to be related to long-term relapse.

Proffit et al. developed a working definition in the assessment of the stability of an orthognathic procedure using the proportion of patients who experienced a clinically significant (≥ 2 mm) relapse. They chose the 2 mm cut-off because relapse of less magnitude could easily

be corrected orthodontically and would not require reoperation. However, caution needs to be taken when generalizing this threshold to all relapse studies until its external validity is proved. Furthermore, creating a dichotomous variable (<2mm relapse; >2mm relapse) from a continuous variable (magnitude of relapse in mm) leads to information loss and reduction of statistical efficacy. Therefore, the relapse was measured and presented as a continuous variable in the current study.

The findings of the present study agree with our clinical experience. Long-term skeletal relapse is often observed in patients with high preoperative mandibular plane angle, who undergo large advancements with counterclockwise rotation of the mandible. It is also reasonable to speculate that there exists an interaction effect among these predictors on relapse. Our second study aims to detect this interaction effect among predictors to better understand their combined influence on relapse.

Conclusion

In conclusion, mandibular plane angle, mandibular advancement, and counterclockwise rotation were independent risk factors for both horizontal and vertical long-term skeletal relapse. Patients with higher preoperative mandibular plane angle, who underwent larger advancements with counterclockwise rotation were predisposed to more long-term skeletal relapse. Although relapse cannot be avoided entirely, understanding the independent risk factors and their contributions will optimize treatment planning and long-term stability. Decreasing counterclockwise rotational movements of the condyle and minimizing changes in

the mandibular plane angle, if clinically acceptable, would result in anticipated stability. In that subset of patients where these movements are unavoidable, relapse needs to be discussed in full preoperatively.

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Tables

Table 1 Demographic and Clinical Characteristics

Variables	Statistics (n=96)	
Female, number(%)	66(68.8%)	
Age, mean±SD, years	29.7±10.5	
Temporomandibular joint symptom, number(%)	60(62.5%)	
Mandibular plane angle, mean±SD, °	33.1±5.7	
Bimaxillary, number(%)	73(76%)	
Counterclockwise rotation, number(%)	60(62.5%)	
Mandibular advancement, mean±SD, mm	8.8±2.4	
Genioplasty, number(%)	67(69.8%)	
Fixation, number(%)		
	Bicortical screws	61(63.5%)
	Miniplates+Monocortical screws	26(27.1%)
	Combination	9(9.4%)
Follow-up, mean±SD, years	3.8±1.8	
Horizontal long-term skeletal relapse, mean±SD, mm	1.6±1	
≥ 2 mm horizontal relapse, number(%)	23(24%)	
Vertical long-term skeletal relapse, mean±SD, mm	0.9±0.7	
≥ 2 mm vertical relapse, number(%)	9(9.4%)	

Table 2 Risk Factors for Horizontal long-term Skeletal Relapse

	Univariate Coefficient	95% CI	P-value	R ²	Multivariate Coefficient	95% CI	P-value
Sex	0.29	-0.13, 0.71	0.177	0.02	-0.09	-0.28, 0.1	0.359
Age	0.02	0.01, 0.04	0.009**	0.07	-0.01	-0.02, -0.001	0.036*
Temporomandibular joint symptom	0.31	-0.09, 0.71	0.131	0.02	0.16	-0.03, 0.34	0.095
Mandibular plane angle	0.11	0.09, 0.14	<0.001***	0.43	0.03	0.01, 0.05	0.001**
Bimaxillary	1.35	0.98, 1.72	<0.001***	0.36	0.31	0.05, 0.56	0.018*
Counterclockwise rotation	0.76	0.38, 1.14	<0.001***	0.15	0.4	0.22, 0.58	<0.001***
Mandibular advancement	0.34	0.3, 0.38	<0.001***	0.75	0.29	0.23, 0.35	<0.001***
Genioplasty	0.97	0.59, 1.35	<0.001***	0.21	-0.22	-0.47, 0.02	0.077
Fixation				0.11			
Miniplates+monocortical screws	reference	reference	reference		reference	reference	reference
Bcortical screws	0.7	0.27, 1.13	0.002**		0.13	-0.06, 0.33	0.183
Combination	0.81	0.09, 1.52	0.027*		0.15	-0.16, 0.47	0.331

CI: confidence interval

* p<0.05, ** p<0.01, *** p<0.001

Table 3 Risk Factors for Vertical long-term Skeletal Relapse

	Univariate				Multivariate		
	Coefficient	95% CI	P-value	R ²	Coefficient	95% CI	P-value
Sex	0.15	-0.14, 0.45	0.312	0.01	-0.04	-0.3, 0.22	0.75
Age	0.01	-0.001, 0.03	0.061	0.04	-0.003	-0.02, 0.01	0.56
Temporomandibular joint symptom	0.01	-0.28, 0.29	0.966	0	-0.06	-0.3, 0.19	0.66
Mandibular plane angle	0.07	0.05, 0.09	<0.001***	0.31	0.05	0.02, 0.07	<0.001***
Bimaxillary	0.36	0.04, 0.67	0.027*	0.05	-0.2	-0.54, 0.15	0.26
Counterclockwise rotation	0.54	0.28, 0.81	<0.001***	0.15	0.34	0.1, 0.58	0.007**
Mandibular advancement	0.14	0.1, 0.19	<0.001***	0.27	0.12	0.04, 0.19	0.005**
Genioplasty	0.28	-0.01, 0.58	0.059	0.04	-0.1	-0.44, 0.24	0.56
Fixation				0.02			
Miniplates+monocortical screws	reference	reference	reference		reference	reference	reference
Bcortical screws	0.2	-0.12, 0.51	0.22		-0.11	-0.38, 0.15	0.394
Combination	0.002	-0.52, 0.52	0.994		-0.22	-0.64, 0.2	0.31

CI: confidence interval;

* p<0.05, ** p<0.01, *** p<0.001

Figures

Figure 1

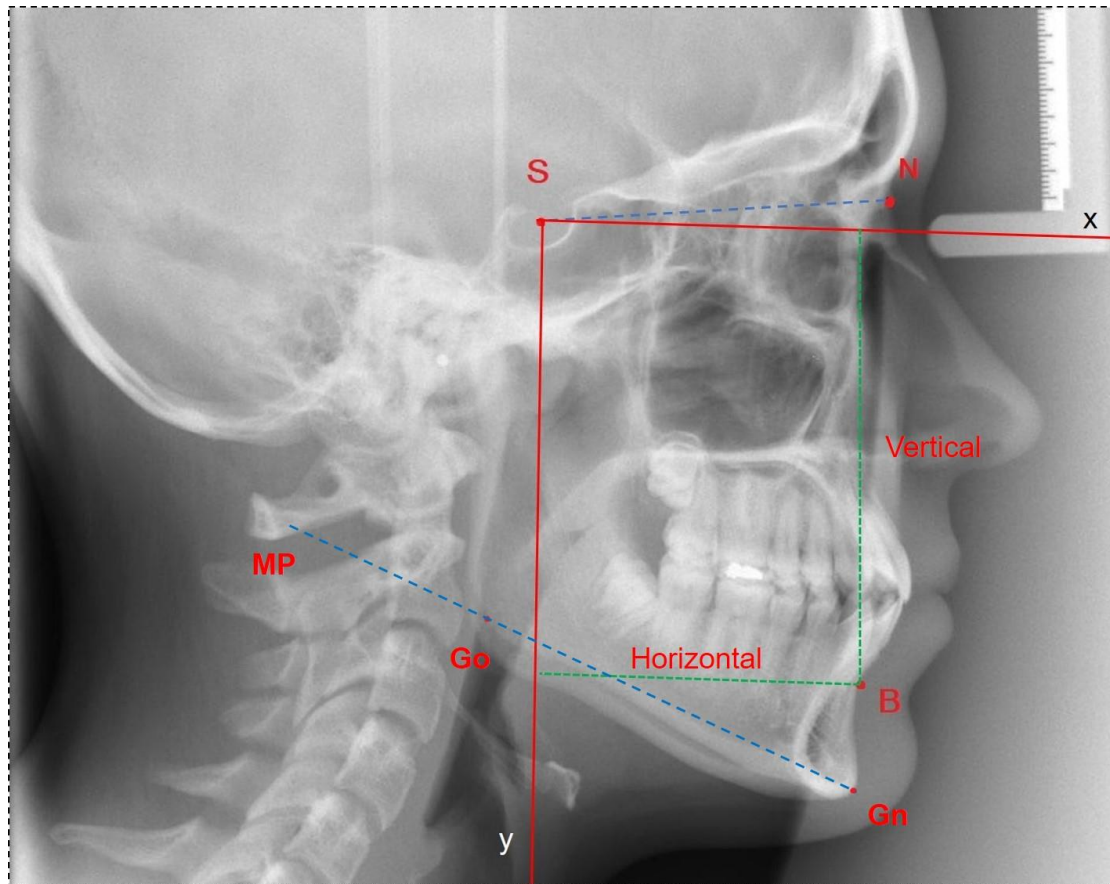


Figure 2 The landmarks and x - y coordinates on lateral cephalogram. The distances from B to the x -axis and y -axis were measured at preoperative (T0), within 1 week postoperative (T1), and a minimum of 2 years postoperative (T2).

S: Sella. N: Nasion. Go: Gonion. Gn: Gnathion. B: B point. Red line x : x -axis, a line through Sella and 7° downward from the Sella-Nasion line. Red line y : y -axis, the line perpendicular to x -axis through Sella. Blue dotted line: MP, Mandibular Plane, a line through Gonion and Gnathion. Green dotted line: Horizontal and vertical position of B-point.

Figure 2

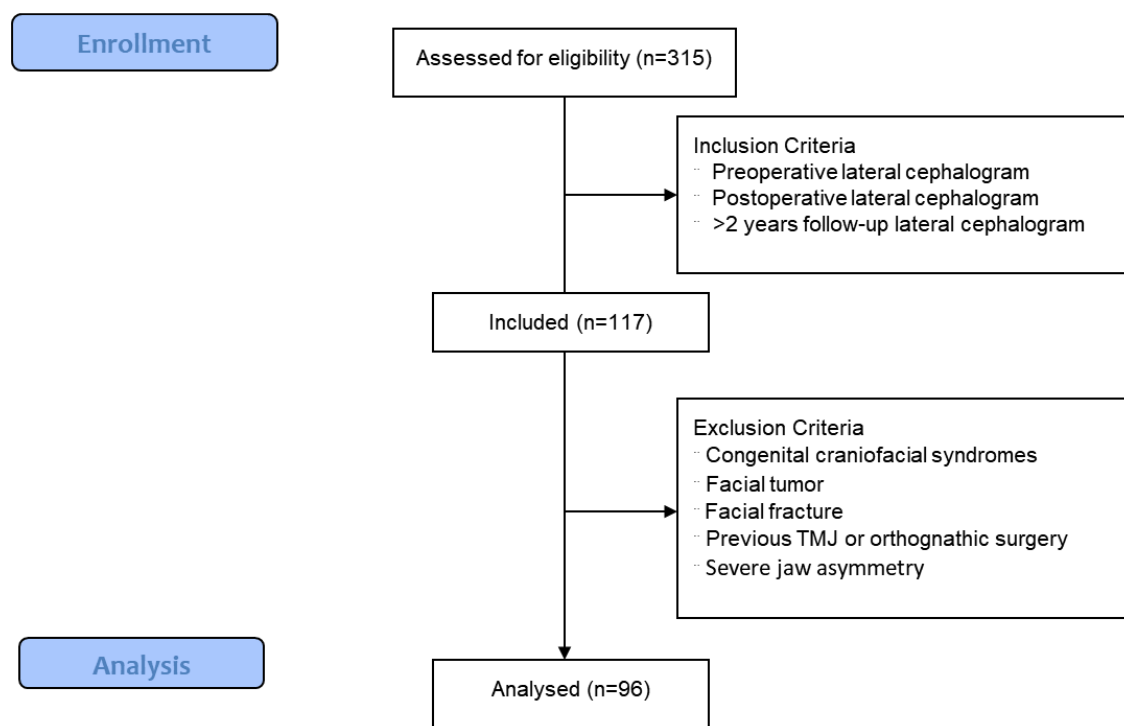


Figure 2 Consort Flow Diagram for Sample Selection.

Figure 3

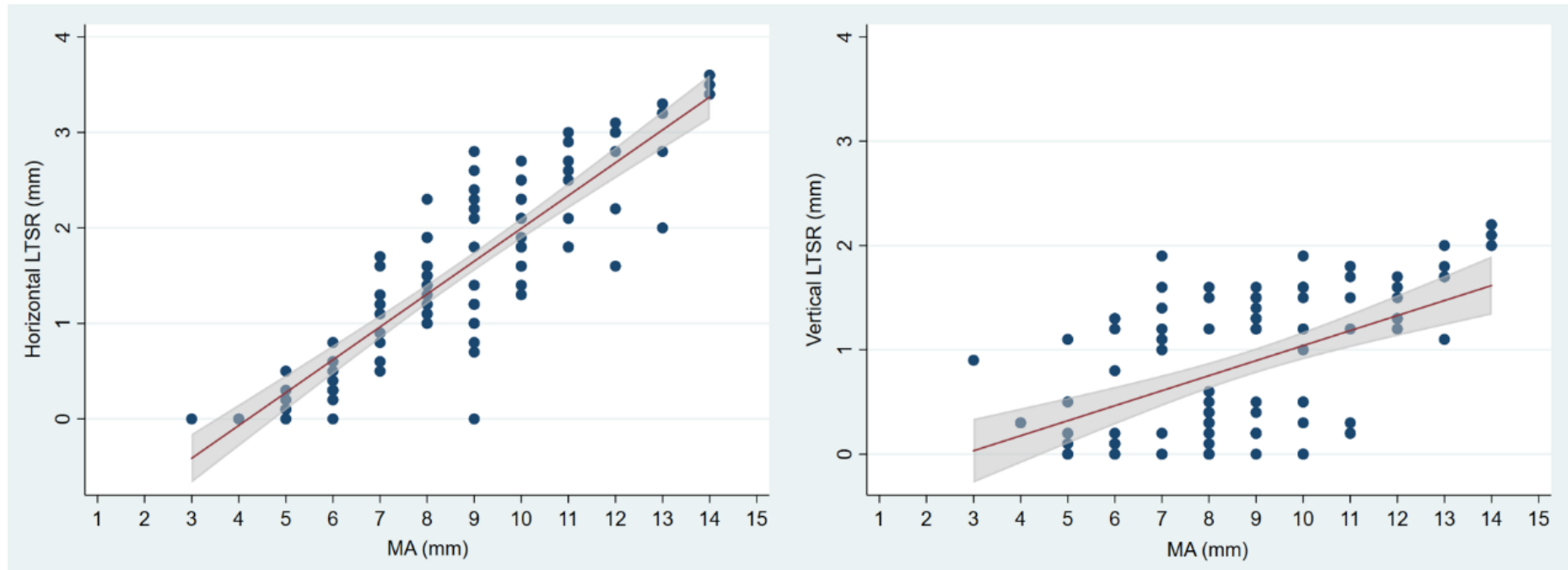


Figure 3 Scatter plots and linear fit lines showed the positive associations between the magnitude of MA and horizontal (left) and vertical (right) long-term skeletal relapse.

Navy circle: long-term skeletal relapses. Maroon line: the linear fit line between mandibular advancement and long-term skeletal relapse. Grey band: 95% confidence interval. LTSR: long-term skeletal relapse. MA: the magnitude of mandibular advancement.

Figure 4

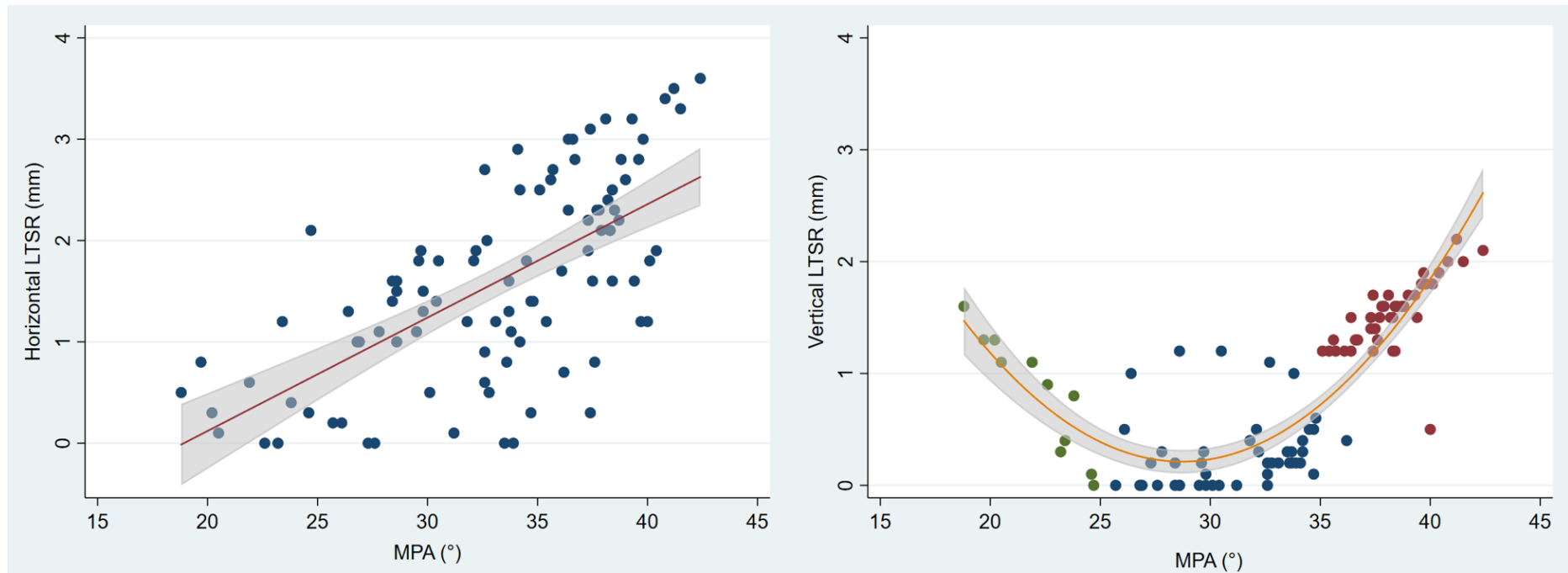


Figure 4: Scatter plot and the linear fit line showed a positive association between mandibular plane angle and the horizontal long-term skeletal relapse (left), as well as a quadratic association between mandibular plane angle and the vertical long-term skeletal relapse (right). Navy circle: long-term skeletal relapses. Maroon line: the linear fit line. Green circle: vertical relapse in low angle group. Maroon circle: vertical relapse in high angle group. Orange line: quadric fit line between mandibular plane angle and vertical long-term skeletal relapse. Grey band: 95% confidence interval. LTSR: long-term skeletal relapse. MPA: preoperative mandibular plane angle.

PAPER 2

Interaction Analysis of Risk Factors for Long-term Skeletal Relapse Following Mandibular Advancement with Bilateral Sagittal Split Osteotomy

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Abstract

This study aims to identify an interaction effect among risk factors for long-term skeletal relapse following mandibular advancement with bilateral sagittal split osteotomy. The study sample consisted of 96 patients who underwent mandibular advancement with bilateral sagittal split osteotomy. Predictor variables analyzed for interaction effect included gender, age, preoperative temporomandibular joint symptoms, mandibular plane angle, single/double jaw surgery, clockwise/counterclockwise mandibular rotation, the magnitude of mandibular advancement, concomitant genioplasty, the type of fixation, and follow-up duration. Multivariable interaction analyses were applied to detect a significant interaction among these risk factors. Stratification analyses and 2-way full factorial interaction analyses were performed to demonstrate how the interaction influenced the associations between covariates and relapse. The interactions of gender and mandibular rotation($p=0.006$), as well as the mandibular plane angle and mandibular rotation($p=0.002$), were statistically significant with horizontal long-term skeletal relapse. No significant interaction for vertical long-term skeletal relapse was identified. The present study shows that females or patients with a mandibular plane angle $\geq 30^\circ$ who underwent counterclockwise mandibular rotation were predisposed to greater horizontal long-term skeletal relapse, compared to those who underwent clockwise rotation. Therefore, we recommend judicious use of counterclockwise rotation to

minimize the relapse, especially in females and patients with high mandibular plane angle.

Introduction

Bilateral sagittal split osteotomy is the most commonly performed surgical procedure for mandibular advancement. However, mandibular advancement with bilateral sagittal split osteotomy is associated with several complications that can affect the clinical outcome and patient satisfaction. One primary concern is the postoperative relapse, which can be categorized as short- or long-term, skeletal or dental and horizontal or vertical depending on timing, anatomic landmark changes and direction of movement. Of these, the long-term skeletal relapse following bilateral sagittal split osteotomy is the most complex and challenging phenomenon involving many interacting risk factors. Potential risk factors have been reported and include: 1) Demographic characteristics, e.g. age, gender, body mass index, bone mineral density); 2) Anatomical factors e.g. preoperative temporomandibular joint pathology, preoperative mandibular/occlusal plane angle; 3) Surgical factors e.g. intraoperative condylar repositioning, single or double jaw surgery, direction of mandibular rotation, change of occlusal or mandibular plan angle, magnitude of mandibular advancement, use of bone grafts, concomitant genioplasty, type and material of internal fixation, and 4) Postsurgical factors e.g. postoperative maxillomandibular fixation, orthodontic treatment, and progressive condylar resorption¹⁻⁷.

In our previous study, we identified preoperative mandibular plane angle, the magnitude of mandibular advancement, and counterclockwise rotation of the mandible

as independent risk factors for both horizontal and vertical long-term relapse. However, only main effects were evaluated in this study. It is reasonable to speculate that there is an effect modification or interaction among these risk factors on relapse. The interpretation of the association between an individual risk factor and relapse is incomplete based on only the main effect if a statistically significant effect modification or interaction exists⁸⁻⁹. Effect modification focuses on whether the relapse of bilateral sagittal split osteotomy differs across different strata of inherent patient characteristics (e.g., age, gender, preoperative temporomandibular joint symptoms, and mandibular plane angle). Interaction aims to assess the joint effect of surgical specifics on relapse (e.g., single or double surgery, clockwise or counterclockwise mandibular rotation, +/- genioplasty). Regardless of the ambiguous terminology, effect modification and interaction are often used interchangeably because both effects are analyzed with marginal structural models¹⁰⁻¹¹. We use the term interaction for both effects throughout the current study.

Interaction analyses have been widely performed in clinical epidemiology when evaluating the associations between multiple predictors and outcome. However, they have not gained popularity in the field of oral and maxillofacial clinical research. Understanding the potential interaction is critical to building a prediction model for relapse. However, to date, no study has investigated the interaction among risk factors on long-term skeletal relapse using appropriate statistical analytic methods.

The purpose of this study is to answer the following research question: Of those risk factors associated with long-term skeletal relapse, is there a significant interaction that would alter their impact on long-term skeletal relapse? We hypothesize that a significant interaction between individual predictors will be found. The specific aims are 1) to detect a significant interaction of 10 predictors(not sure why we have 10 in the second study and only 9 in the first?) on long-term skeletal relapse; 2) to show how the interaction influences the associations between predictors and relapse.

Materials and Methods

Study Design and Sample

To answer our research question, we utilized the dataset from our previous retrospective cohort study, which was composed of 96 patients who underwent mandibular advancement with bilateral sagittal split osteotomy in the Department of Oral and Maxillofacial Surgery at Massachusetts General Hospital from June 1, 2005, through June 1, 2017. Inclusion required complete medical and radiographic records including preoperative, within 1 week postoperative, and a minimum of 2 years postoperative lateral cephalograms. Study approval was obtained from the Partners Institutional Review Board (Protocol number 2017P002223).

Study Variables

Predictor variables included: 1) gender; 2) age at surgery; 3) preoperative temporomandibular joint symptoms; 4) preoperative mandibular plane angle; 5) single or double jaw surgery; 6) the direction of mandibular rotation; 7) the magnitude of mandibular advancement; 8) concomitant genioplasty; 9) the type of fixation, and 10) follow-up period. Temporomandibular joint symptoms were defined as the presence of one or more of the following: locking, crepitus, clicking, arthralgia, pain in the masticatory muscles, disc displacement/dislocation, and limitation in mandibular movement. Mandibular plane angle was defined as the angle between the Sella-Nasion line and the mandibular plane (Gonion-Gnathion line) measured on the preoperative lateral cephalograms. Double jaw surgery was defined as maxillomandibular advancement with a combination of bilateral sagittal split osteotomy and Le Fort I osteotomy. The direction of mandibular rotation included clockwise rotation or counterclockwise rotation of the mandible. The magnitude of mandibular advancement was measured intraoperatively and verified by measuring the positional change at B point from preoperative to within 1-week postoperative lateral cephalograms. Concomitant genioplasty was defined as either genial tubercle advancement or advancement genioplasty. The types of fixation included miniplates+monocortical screws, bicortical screws, or hybrid techniques using a combination of both. The

follow-up period was recorded from the date of surgery to the date of the last cephalogram.

The primary and secondary outcome variables were the horizontal and vertical long-term skeletal relapse, respectively. These were defined as the horizontal and vertical changes of the B-point on a minimum 2-year postoperative versus within 1-week postoperative lateral cephalogram. The positional change was defined as relapse only if the B-point moved in the opposite direction to the initial surgical movement.

Statistical Analyses

Continuous variables (age, mandibular plane angle, mandibular advancement, follow-up, horizontal and vertical long-term skeletal relapse) were expressed as means $\pm$ standard deviations. Categorical variable (fixation methods) or dichotomous variables (gender, +/- temporomandibular joint symptom, single or double jaw surgery, clockwise or counterclockwise rotation, +/- genioplasty) were reported as proportions or percentages. Continuous variables were further categorized for stratification analyses. Specifically, age was dichotomized into age $\leq$ 20 years or age $>$ 20 years. Preoperative mandibular plane angle was categorized as low ($<25^\circ$), medium (between 25° and 35°) and high ($>35^\circ$) groups. The magnitude of mandibular advancement was dichotomized into mandibular advancement $\leq$ 8 mm or $>$ 8 mm. Follow-up duration was categorized into 2-3 years, 3-4 years, 4-5 years, and $>$ 5 years. Comparisons between two groups were performed using t-testing or Chi-square testing depending on the type of variables.

To identify a significant interaction effect, we initially evaluated all 45 pairs of 10 predictor variables using multivariable fractional polynomial interaction analysis to adjust for covariates. We then performed 2-way full factorial interaction analyses including a significant interaction term and other covariates in multivariate linear regression models using horizontal and vertical relapse as dependent variables, respectively. Higher-dimensional interaction (including 3 or more variables) were inspected if significant 2-way interactions were detected. For vertical relapse, we included both an interaction term and a polynomial term of mandibular plane angle because a quadratic association between mandibular plane angle and vertical relapse was identified in our previous study. *Margins* and *margins plots* were used to calculate and visualize the predicted relapse. A p-value < 0.01 was used in detecting statistically significant interaction and a p-value < 0.05 was considered statistically significant elsewhere. Statistical analysis was done using STATA v15.1 (StataCorp LLC, College Station, Texas, USA). The results of regression analyses are presented as coefficients with corresponding 95% confidence intervals and p-values.

Results

Stratification Analyses and Interaction Identification

Stratification analyses showed the unadjusted difference in horizontal relapse between patients who underwent clockwise and counterclockwise rotation was statistically significant in females, in patients >20 years old, in patients with preexisting

temporomandibular joint symptom, in those with medium or high mandibular plane angle, in cases of bimaxillary advancements, with mandibular advancement > 8 mm, with or without genioplasty, and in patients who underwent internal fixation using bicortical screws ([Table 1](#)). The overall effect difference between counterclockwise and clockwise rotation was 0.8 mm (95% CI: 0.4, 1.1, $p=0.0001$). After adjustment for covariates, only the interaction of mandibular rotation and gender (coefficient=0.47, 95% CI: 0.14, 0.81, $p=0.006$), as well as mandibular rotation and mandibular plane angle (coefficient=0.05, 95% CI: 0.02, 0.07, $p=0.002$) were statistically significant for horizontal long-term skeletal relapse among all 45 pairs of 10 predictors. No significant interaction for vertical long-term skeletal relapse was identified. High-dimensional interactions evaluating gender, mandibular plane angle, and direction of mandibular rotation showed no statistical significance.

Interaction of Mandibular Rotation and Gender

[Figure 1A](#) illustrates the horizontal long-term skeletal relapse in patients with different gender and direction of mandibular rotation. We observed an average horizontal long-term skeletal relapse of 1.3 mm in 14 males with clockwise rotation, 1.5 mm in 16 males with counterclockwise rotation, 1 mm in 22 females with clockwise rotation, and 2 mm in 44 females with counterclockwise rotation. [Figure 1B](#) shows a significant interaction effect between mandibular rotation and gender on horizontal relapse. The average predicted horizontal relapse was 1.54 mm in males with clockwise

rotation, 1.64 mm in males with counterclockwise rotation, 1.2 mm in females with clockwise rotation, and 1.77 mm in females with counterclockwise rotation. The difference of horizontal relapse between counterclockwise and clockwise rotation in males was minor and insignificant (0.1 mm, 95% CI: -0.17, 0.37, $p=0.47$). However, in female patients who underwent counterclockwise rotation, we would expect a significant increase of horizontal long-term skeletal relapse (0.57 mm, 95% CI: 0.36, 0.78, $p<0.001$) compared to clockwise rotation.

Interaction of Mandibular Rotation and Mandibular Plane Angle

Figure 2A demonstrates positive associations between horizontal relapse and preoperative mandibular plane angle in patients who underwent clockwise and counterclockwise rotation in our cohort. **Figure 2B** shows a significant interaction between mandibular rotation and preoperative mandibular plane angle on horizontal relapse. The difference in predicted horizontal relapse between patients who underwent counterclockwise vs. clockwise rotation was -0.4 mm when mandibular plane angle=15° (95% CI: -0.9, 0.1, $p=0.15$); -0.2 mm when mandibular plane angle=20° (95% CI: -0.5, 0.2, $p=0.43$); 0.1 mm when mandibular plane angle=25° (95% CI: -0.2, 0.3, $p=0.58$); 0.3 mm when mandibular plane angle=30° (95% CI: 0.1, 0.5, $p=0.001$); 0.5 mm when mandibular plane angle=35° (95% CI: 0.3, 0.7, $p<0.001$); 0.8 mm when mandibular plane angle=40° (95% CI: 0.5, 1, $p<0.001$); 1 mm when mandibular plane angle=45° (95% CI: 0.6, 1.4, $p<0.001$). Patients with a mandibular plane angle $\geq 30^\circ$ who underwent

counterclockwise rotation were predisposed to greater horizontal relapse compared to clockwise rotation.

Discussion

The results of the present study show significant interactions between mandibular rotation and gender, as well as mandibular rotation and mandibular plane angle on horizontal long-term skeletal relapse. Due to these interaction effects, females or patients with mandibular plane angle $\geq 30^\circ$ undergoing counterclockwise mandibular rotation are predisposed to greater horizontal relapse as compared to the clockwise mandibular rotation.

Counterclockwise Rotation

To establish functional and esthetic surgical results, counterclockwise rotation of distal segments is commonly performed with bilateral sagittal split osteotomy advancement to close an anterior open bite and reduce the anterior facial height in patients with severe mandibular retrognathia. In most cases, the proximal segments are also rotated counterclockwise to line up the inferior border, though the magnitude of rotation may be different between segments.

Condylar resorption, characterized by progressive morphologic, volumetric and positional changes of the condyle, is believed to be the major and direct cause of long-term relapse. Multiple authors have reported a positive correlation between

counterclockwise rotation and condylar remodeling/resorption, as well as subsequent relapse due to the following: 1) Counterclockwise rotation of the proximal segments directly inclines the condyle posteriorly, thereby exposing the less dense, previously unloaded anterior-superior surface of the condyle to compressive loading; 2) Counterclockwise rotation generates wider displacement between mandibular segments, stretching both muscle and soft tissue; 3) The altered orientation and increased tension of the soft tissue pulls the mandible posteriorly and inferiorly; 4) The soft tissue tension adds extra loading on the vulnerable condylar surfaces; 5) The neuromuscular adaptation may also be delayed due to the stretched soft tissue.¹²⁻¹⁷

Interaction of Gender*Direction

A predisposition to condylar remodeling/resorption and relapse after bilateral sagittal split osteotomy in females who underwent counterclockwise rotation has been noted by several authors. Valladares-Neto et al.¹⁸ concluded that young females who underwent counterclockwise rotation were prone to postoperative condylar resorption and relapse. Xi et al.¹⁹ highlighted the remarkable impact of female gender and counterclockwise rotation on postoperative condylar volume and stability. Their second study²⁰ showed significantly smaller preoperative condyles, higher risk and greater amount of volume reduction, and more horizontal skeletal relapse in females. They suggested a stronger effect of condylar resorption on relapse in females compared to

males. Gunson et al.²¹ noted that the increased estrogen receptors in female temporomandibular joints might play a role in condylar remodeling/resorption.

Although both female gender and counterclockwise rotation were reported to be related to relapse, the interaction between gender and mandibular rotation has not been previously identified. Our results indicate that the effect of mandibular rotation on horizontal long-term skeletal relapse is modified by the patient gender. Females who undergo counterclockwise rotation are predisposed to more significant horizontal long-term skeletal relapse. A speculative reason may be that the condylar response to increased loading is exaggerated in females, leading to greater condylar resorption and relapse.

Interaction of Mandibular plane angle*Direction

The influence of preoperative mandibular plane angle on relapse remains controversial. High preoperative mandibular plane angle has been described as a risk factor for condylar resorption and relapse, particularly on patients who had counterclockwise rotation to close the anterior open bite. Mobarak et al.²² compared the postoperative stability in 20 patients with a high angle of average 43° to 20 patients with a low angle of average 20.8° during 3-year follow-up after bilateral sagittal split osteotomy mandibular advancement. The former group demonstrated both higher frequency and a more considerable amount of horizontal relapse. Eggensperger et al.²³ reported that 6 patients with mandibular plane angle > 30° had 3.3 mm relapse at 12-

year postoperatively, whereas 4 patients with mandibular plane angle $< 20^\circ$ demonstrated no notable long-term relapse. Ow et al.²⁴ systematically reviewed 222 patients from 9 articles who underwent bilateral sagittal split osteotomy and were followed for 6 to 12 months. They concluded that patients with high mandibular plane angle showed greater skeletal relapse compared with medium angle patients during this time frame. Joss and Vassalli²⁵ suggested that high angle patients had a more horizontal relapse, whereas low angle patients had a more vertical relapse. Schwartz et al.²⁶ noted that patients with mandibular plane angle $\geq 37^\circ$ or $< 27^\circ$ displayed more substantial relapse compared to patients with a medium angle (between 27° and 37°) 18 months after an average advancement of 11.6 mm.

The present study demonstrates that patients with mandibular plane angle $\geq 30^\circ$ who undergo counterclockwise rotation are prone to more horizontal relapse compared to clockwise rotation. A reasonable explanation may be that high angle patients often have slender, finger-shaped, and posteriorly inclined condyles with less dense bone trabeculae, making it more difficult to resist the additional load generated by counterclockwise rotation.

Study Strength

To date, our study is the first to identify and analyze the interaction effect among multiple predictors and relapse using appropriate statistical analytic methods. Although the sample size based on a single center retrospective cohort did not guarantee an

accurate prediction, the results improve our understanding of associations among individual predictors and relapse. In addition, the multivariate model incorporating the interaction term of gender and mandibular rotation presented an Akaike information criterion (AIC) of 90.2 and Bayesian information criterion (BIC) of 123.6, whereas the model with an interaction term of mandibular plane angle and mandibular rotation displayed an AIC of 88.3 and BIC of 121.6. Both compared favorably to the model without the interaction term (AIC: 97.1, BIC: 127.9).

Study Limitations

This retrospective cohort study has several limitations, which require readers to be cautious when interpreting results. A general issue is sample size and power. It is suggested that the sample size to detect an interaction is higher than that needed to detect the main effect. Therefore, we may identify more statistically significant interactions given a larger sample. Another concern is that the effect on relapse cannot be fully understood unless all potential risk factors are included. For example, dedicated preoperative temporomandibular joint imaging was frequently unavailable in these patients, making it difficult to assess the critical role of preexisting temporomandibular joint pathology in the postoperative instability. Furthermore, no hormone testing or radiographical and biomechanical assessment of the condyles were performed, so inferences about the underlying mechanism of the identified interactions are speculated based on the results in the literature.

Multicollinearity might be another concern because several predictors could correlate with each other. In the model with an interaction term of gender*mandibular rotation, only moderate multicollinearity was observed with each predictor having a variance inflation factor (VIF) <5. However, the model with the interaction term of mandibular plane angle*mandibular rotation displayed severe multicollinearity. The multicollinearity can be explained from both clinical and statistical perspectives. Clinically, high angle patients often require counterclockwise rotation. Statistically, interaction terms produce multicollinearity because these terms include the main effects.

The limitations of multiple interaction analyses include false positives due to multiple comparisons, and limited external validity to facilitate individual treatment decisions because patients have different characteristics. To solve multiple testing problem during interaction analyses, we used multivariable fractional polynomial interaction analysis with a significance level of 1%.

External validity refers to the question of whether our results are generalizable to patients other than the population in our study. The only formal way to establish the external validity would be to repeat the study for that specific target population. Judging the external validity of study results cannot be done by applying given eligibility criteria to a single target population. Rather, it is a complex reflection in which prior knowledge, statistical considerations, biological plausibility and eligibility criteria all have a place. Therefore, we are going to design and implement a multicenter study going forward to test the validity of our results.

Conclusion

In summary, we found significant interactions between the direction of mandibular rotation and gender, as well as the direction of mandibular rotation and mandibular plane angle on horizontal long-term skeletal relapse. Due to the interaction effects, females or patients with mandibular plane angle $\geq 30^\circ$ who undergo counterclockwise rotation are predisposed to have a significantly greater horizontal long-term skeletal relapse. Therefore, we recommend judicious use of counterclockwise rotation to minimize the risk of long-term relapse, especially in females and patients with high mandibular plane angle.

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Tables

Table 1 Stratification and Interaction Analyses of Horizontal Long-term Skeletal Relapse in Patient Who Underwent Clockwise vs. Counterclockwise rotation

Variables		Horizontal LTSR (mm)				Interaction	
		CR(n=36)	CCR(n=60)	Contrast	95% CI	P-value	P-value
Gender	Male(n=30)	1.3±0.7(n=14)	1.5±0.9(n=16)	0.2	-0.5, 0.8	0.6	0.006**
	Female(n=66)	1±0.7(n=22)	2±1(n=44)	1	0.6, 1.5	0.0001***	
Age	≤20(n=19)	1.1±0.7(n=9)	1.7±1(n=10)	0.6	-0.3, 1.4	0.2	0.1
	>20(n=77)	1.1±0.7(n=27)	1.9±1(n=50)	0.8	0.4, 1.2	0.0004***	
TMJ symptoms	With TMJ symptoms(n=60)	1.1±0.7(n=20)	2±1(n=40)	0.9	0.5, 1.5	0.0003***	0.4
	Without TMJ symptoms(n=36)	1.2±0.8(n=16)	1.6±0.9(n=20)	0.4	-0.2, 1	0.2	
MPA	Low(n=11)	0.9±1(n=4)	0.4±0.3(n=7)	-0.5	-1.3, 0.4	0.3	0.002**
	Medium(n=45)	1±0.6(n=24)	1.4±0.8(n=21)	0.4	0.1, 0.9	0.03*	
	High(n=40)	1.7±0.6(n=8)	2.5±0.7(n=32)	0.8	0.2, 1.3	0.009**	
Single or Double	Single(n=23)	0.3±0.4(n=9)	0.7±0.5(n=14)	0.4	-0.1, 0.8	0.1	0.1
	Double(n=73)	1.4±0.6(n=27)	2.2±0.8(n=46)	0.8	0.5, 1.2	<0.001***	
MA	≤8(n=44)	0.7±0.6(n=20)	1±0.7(n=24)	0.3	-0.1, 0.7	0.1	0.1
	>8(n=52)	1.6±0.6(n=16)	2.4±0.8(n=36)	0.8	0.4, 1.3	0.0002***	
Genioplasty	With Genioplasty(n=67)	1.4±0.6(n=27)	2.2±0.9(n=40)	0.8	0.5, 1.2	0.0001***	0.2
	Without Genioplasty(n=29)	0.3±0.5(n=9)	1.2±0.8(n=20)	0.9	0.3, 1.4	0.007**	
Fixation	Miniplates+Monocortical screws(n=26)	0.9±0.7(n=9)	1.1±0.9(n=17)	0.2	-0.6, 0.9	0.6	0.5
	Bicortical screws(n=61)	1.2±0.7(n=23)	2.1±0.9(n=38)	0.9	0.5, 1.4	<0.001***	
	Hybrid(n=9)	1.2±0.8(n=4)	2.4±0.8(n=5)	1.2	-0.04, 2.4	0.06	
Follow-up	2-3 years(n=34)	0.9±0.9(n=13)	1.2±0.7(n=21)	0.3	-0.3, 0.8	0.3	0.3
	3-4 years(n=28)	1.3±0.8(n=11)	1.3±0.8(n=17)	0.001	-0.6, 0.7	0.9	
	4-5 years(n=13)	1.5±0.5(n=4)	2±0.9(n=9)	0.5	-0.5, 1.6	0.3	
	>5 years(n=21)	2.8±0.6(n=8)	2.4±0.9(n=13)	-0.4	-1.1, 0.4	0.3	
	Horizontal LTSR	1.1±0.7(n=36)	1.9±1(n=60)	0.8	0.4, 1.1	0.0001***	

CR: clockwise rotation; CCR: counterclockwise rotation; TMJ: temporomandibular joint; MPA: mandibular plane angle; MA: mandibular advancement; LTSR: Long-term skeletal relapse.

Figures

Figure 1

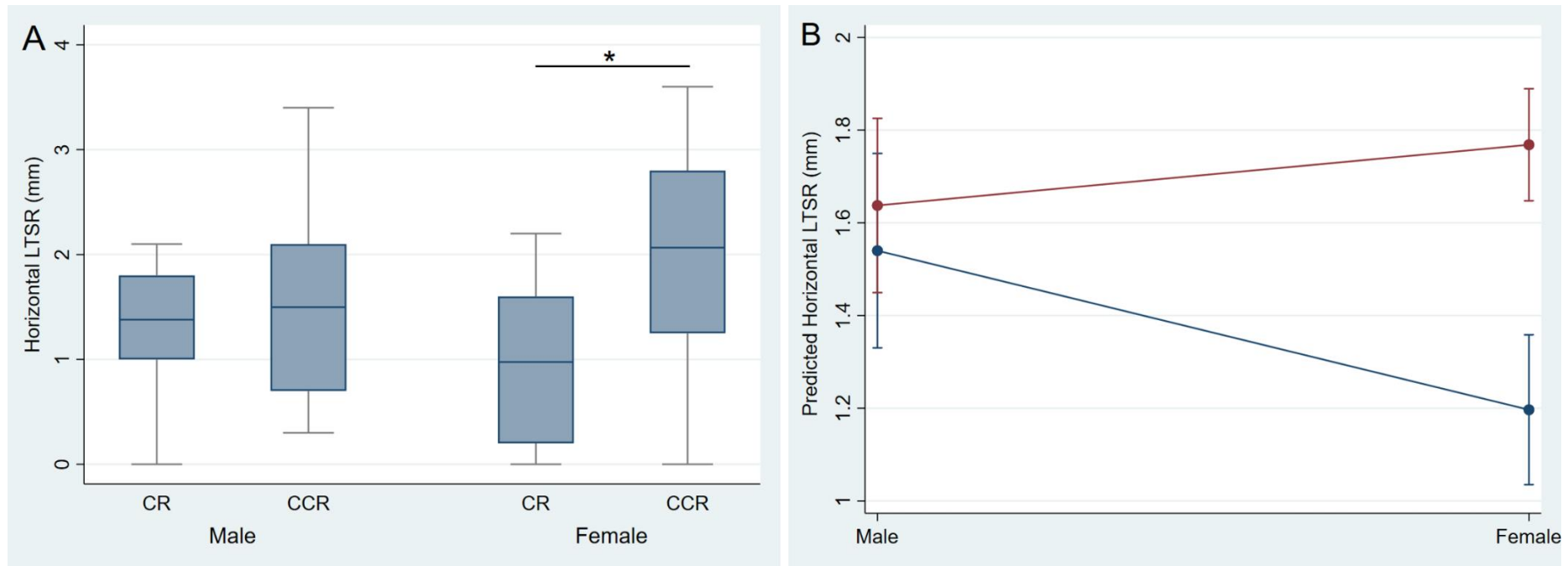


Figure 1A The horizontal long-term skeletal relapse in patients of different gender with different direction of mandibular rotation. **Figure 1B** The significant interaction effect between mandibular rotation and gender on horizontal long-term skeletal relapse. Females who underwent counterclockwise rotation were predisposed to more horizontal relapse as compared to clockwise rotation. LTSR: long-term skeletal relapse, CR: clockwise rotation, CCR: counterclockwise rotation.

Figure 2

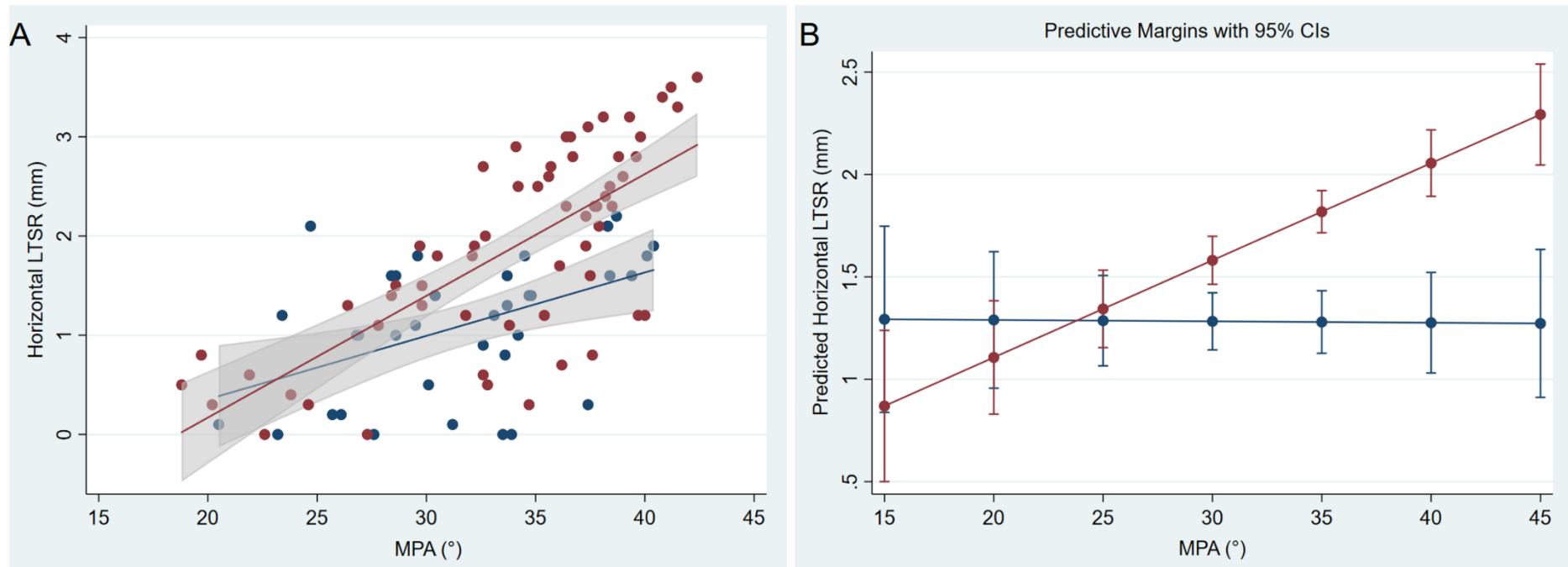


Figure 2A Positive associations between horizontal long-term skeletal relapse and preoperative mandibular plane angle in patients who underwent clockwise vs. counterclockwise rotation in our cohort. **Figure 2B** The significant interaction between mandibular rotation and preoperative mandibular plane angle on horizontal long-term skeletal relapse. Patients with mandibular plane angle $\geq 30^\circ$ who underwent counterclockwise rotation were prone to more horizontal long-term skeletal relapse as compared to clockwise rotation.

LTSR: long-term skeletal relapse, MPA: mandibular plane angle

SUMMARY

In summary, the results of the first study demonstrated that mandibular plane angle, the magnitude of mandibular advancement, and counterclockwise mandibular rotation were independent risk factors for both horizontal and vertical long-term skeletal relapse. Patients with higher mandibular plane angle, who underwent larger advancement with counterclockwise rotation were predisposed to more long-term skeletal relapse. Although long-term skeletal relapse cannot be avoided entirely, understanding the independent risk factors and their contributions will optimize treatment planning and long-term stability.

The results of the second study showed significant interactions between mandibular rotation and gender, as well as mandibular rotation and mandibular plane angle on horizontal long-term skeletal relapse. Due to these interaction effects, females or patients with mandibular plane angle $\geq 30^\circ$ who underwent counterclockwise mandibular rotation were predisposed to greater horizontal long-term skeletal relapse as compared to the clockwise mandibular rotation. Therefore, we recommend judicious use of counterclockwise rotation to minimize the risk of long-term skeletal relapse, especially in females and patients with high mandibular plane angle.

DISCUSSIONS AND PERSPECTIVES

We have included common and important risk factors reported to be associated with relapse in this multivariate analysis. Although this was a single-center retrospective study, we had a relatively large sample size with long follow-up compared to existing literature. Also, our study is the first to identify and analyze the interaction effect among multiple predictors and relapse using appropriate statistical analytic methods. The results improve our understanding of associations among individual predictors and relapse.

However, being retrospective in design, this study had several inherent limitations. Although the follow-up duration was consistently greater than 2 years (average 3.8 years), it was still not enough for relapse study because relapse might continue to occur up to 5 years postoperatively. In addition, many details of the surgical and orthodontic treatment were unknown based on a retrospective study. The effect on relapse cannot be fully understood unless all potential risk factors are included. For example, dedicated temporomandibular joint imaging records were not available to analyze the presence and specific diagnoses of preexisting pathology. Furthermore, no hormone testing or radiographical assessment of the condyles were performed, so inferences about the underlying mechanism of the identified interactions are speculated based on the literature. Multicollinearity might be another concern because several predictors could correlate with each other.

The varying length of follow-up may be related to the relapse. Therefore, the time course of relapse development is particularly of interest in the assessment of

postoperative stability. We will perform a prospective longitudinal study with close follow-up in the future to validate the results of the present studies.