Dear Editor,

We are grateful to the reviewers for their insightful feedback and the time they devoted to reviewing our manuscript. We have carefully considered their comments and have made the necessary revisions to the manuscript. We greatly appreciate the time and effort the reviewers invested in improving our work.

Letter to Reviewer #1

1. First Comments of Reviewer #1

[Reviewer's Comment]:
I have read the manuscript “Asian and European craniofacial Class III phenotype: two sides of the same coin?”. This is an interesting study that explores Class III specific phenotypes patterns in different populations. However, I have few suggestions in the current form of the manuscript. The title and aim say “Asian and European”, but the manuscript includes only South-Korean and Spanish participants, that do not represent all Asians and Europeans. Therefore, I suggest to be more specific and realistic in the title and aim.

Were they orthodontic patients? Is there any selection bias of this patients for orthodontic treatment that could reflect in the result?

In the exclusion criteria, were patients with non-syndromic oral cleft included? Also, this sentence belongs to the methods “Non-Spanish and non-South Korean participants were excluded from our analyses to ensure the homogeneity of each cohort”. Please correct: A total of 300 participants exhibiting skeletal Class III malocclusion met our selection criteria: 112 and 188 patients constituted the South European AND East Asian cohort, respectively.

The images in the Fig 1, 3 were to small and difficult to read and interpret. The discussion should be more clear about the limitations of the study and future directions.

Response to Reviewer #1: Regarding the first comments made by Reviewer 1, we appreciate the important aspects pointed out. The title has been changed as suggested. Non-syndromic oral cleft patients were not included, and the text has been modified to clarify this aspect. Participants were orthodontic patients indeed, only patients who needed the X-ray for treatment were included for ethical reasons. Patients affected by skeletal class III were selected from all over the country from private and public institutions in order to obtain a well-represented sample of class III subjects in the region. To this respect, we have added a text in the Discussion to clarify this aspect. An independent file is provided, including an original version (non-compressed .pdf version) of “Figures 2 and 3”. Finally, limitations and future directions have been specified in a clearer manner.

[Revised Text]
“East-Asian and Southern-European craniofacial Class III phenotype: two sides of the same coin?”
“Eligible participants had to meet the following selection criteria: absence of severe facial trauma, lack of any craniofacial syndromic and non-syndromic conditions, final stage or completed growth upon lateral radiograph imaging, i.e., cervical vertebral maturation stage (CVMS).”

“To ensure ethical considerations, only patients who required X-rays for treatment were selected from private and public institutions in the region. Several studies have shown that patients with Class III malocclusions might be more inclined to opt for orthodontic treatment as the implication for patients tend to be more severe [10].”

“This study aimed to develop a more comprehensive characterisation and further classification of skeletal Class III malocclusions. Nonetheless, there are limitations to consider. Our reliance on two-dimensional cephalometric data, while common in clinical practice and large-scale data collection, may not capture the full range of craniofacial variation (Naqvi et al., 2022). Additionally, future analyses could benefit from measurement methods that are not influenced by sexual dimorphism to enrich interethnic characterisation and comparison (de Frutos-Valle et al., 2020; Yang et al., 2022).”

We are thankful for the positive and insightful comments provided by Reviewer 1. We appreciate the time and effort invested in reviewing our manuscript, which aided us in enhancing the quality of the paper. We have taken into consideration the comments and revised the manuscript accordingly.

Letter to Reviewer #2

1. First comment of Reviewer #2

I have read the submitted research report carefully, and here I am offering my assessment and comments.

The authors stated that Skeletal Class III phenotype is a heterogeneous condition in populations of different ethnicity. Therefore, they aimed to analyse the joint and ethnicity-specific clustering of morphological features of skeletal class III patients of Asian and European origin. They used a cross-sectional study involved South-Korean and Spanish participants that fulfilled the cephalometric, clinical, and ethnic-related selection criteria. Radiographic records were standardized, calibrated, and measured. 54 skeletal variables were selected for Varimax Factorial Analysis (VFA). Afterward, cluster analysis (CA) was performed (mixed method: k-means and hierarchical clustering). Method error and precision were assessed using ICC, Students’ t-test, and Dahlberg formula. The authors studied and analysed the recorded variables on 285 Korean and Spanish participants exhibiting skeletal Class III malocclusion. They claimed that after performing VFA and CA, the joint sample disclosed three global clusters, and ethnicity-specific analysis revealed four Korean and five Spanish clusters. Cluster_1_global was predominantly Spanish (79.2%), male (83.01%), and was characterized by a predominantly mesobrachycephalic pattern, a larger cranial base, maxilla, and mandible. Cluster_2_global and Cluster_3_global were mainly South Korean (73.9% and 75.6%, respectively) and depicted opposite phenotypes of mandibular projection and craniofacial pattern. The authors concluded that a distinct distribution of Spanish and South Korean participants was observed in the global analysis. Interethnic and interethnic differences were observed, primarily on cranial base and maxilla size, mandible projection, and craniofacial pattern. Finally, they stated that accurate phenotyping reflecting the complexity of SCIII phenotype across diverse populations is critical for improving diagnostic predictability and future personalized treatment protocols.

Overall, the aim of the study is appropriate, and the expected obtained results will shed light and add value to a better understanding of the complexity of Skeletal Class III (SCIII). The authors used well-defined selection criteria for patients and included them in the study, as well as exclusion criteria for participants. The sample size of participants was calculated and found to be a minimum of 85 participants per group was determined considering a 95% confidence level. In the study, the authors used 99 Spanish patients, including 61 males and 38 females, and 186 Korean patients, including 101 males and 85 females.

Unfortunately, the full details, including the age (young, teenage, and elderly) of each group of participants, are missing. Age is a crucial cofounder factor affecting the whole analysis and expected obtained results. I expect that performing the study
analysis based on these assigned groups will provide different, better, and more accurate results. Performing the analysis without considering these cofounders could mislead and confuse the results and interpretations.

The estimated sample size was calculated, assuming two groups of patients, i.e., Spanish and Korean, and two sexes, i.e., males and females, were included in the study. I trust that if the authors include the age as other groups, the required sample size (power of the analysis) will be affected and be different from the currently estimated number.

I recommend reanalysing the data based on their ethnic groups, sex, age per group (young, teenage, and elderly), and interactions between age, sex, per ethnic groups.

Response to Reviewer #2:
Regarding the comments raised by Reviewer 2, we appreciate Reviewer’s comment about these important aspects. As rightly pointed out by the Reviewer, age can be a crucial confounding factor affecting the analysis and the results. To this respect, we have used a radiological indicator of skeletal maturity (Baccetti et al., 2005) as a discriminating factor instead of using the chronological age. In addition, age mean and standard deviation have been included in Table 1. (Results; Table 1) in order to describe and analyse the clusters’ results.

Reference:

2. Minor Comments:

1. Please define the abbreviation of SCIII the first time you present it in the text.
2. The report needs English language and grammatical editing and is approved by a native English speaker.
3. Results in Figures 1 and 3 are not readable, and the authors must present the results in another format, so it will be possible to view them.

Finally, based on these comments, I recommend to major revision of the manuscript.

Response to Reviewer #2: Regarding the minor comments made by Reviewer #2, the abbreviation of SCIII has been removed and replaced by “skeletal class III”, to enhance consistency in the text. The manuscript has been thoughtfully revised to improve language and grammatical editing by a native reviewer. An independent file is provided including an original version (non-compressed .pdf version) of “Figure 2 and 3”.

We appreciate the positive and constructive comments made by Reviewer 2, and we are grateful for the time spent reviewing our manuscript that has helped to improve the quality of our paper. We have modified the manuscript accordingly.

We would like to express our sincere appreciation to the Reviewers for the time and effort dedicated to improving our manuscript. We believe that the revisions made have significantly enhanced the quality and clarity of our work.

Thank you for your consideration.