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Reviewer A

Comment 1: I present to the authors some questions and suggestions.

- Page 3, line 18 (material and methods)- It is described that the study period was from March 2017 to March 2022. However, on page 7, line 5, the period described was from March 2017 to December 2021. What was the correct period?

Reply 1: Thanks for the pointing out the mistyping. I am sorry for the mistyping. the period in the main manuscript is correct. We correct the period in the abstract.

Changes in the text: From March 2017 to December 2021... (line 18 in page 3)

Comment 2: - Page 7 (material and methods)- It would be important to detail the surgical technique. "All subjects underwent bilateral endoscopic sympathicotomy". The abstract is more detailed than the article (page 3, line 19,20).

Reply 2: Thanks for your comments. I more detailed the surgical techniques like abstract.

Changes in the text: All subjects underwent bilateral endoscopic sympathicotomy with or without the expansion of sympathicotomy. T2 and T3 sympathicotomy were routinely performed in patients with craniofacial and palmar hyperhidrosis, respectively. In the expansion sympathicotomy, we expanded the level of sympathicotomy to levels ranging from R5 to R12 by chain ablation to prevent compensatory while avoiding injury to the splanchnic nerves. (line 17-21 at page 8)

Comment 3: - Page 3, line 20- it is described "sympathicotomy with or without the expansion of sympathicotomy", What is expansion of sympathicotomy? More extensive resection of the sympathetic? It should be defined in the text.

Reply 3: Thanks for raising basic questions. Our technique includes the expansion of the levels of sympathicotomy to decrease compensatory hyperhidrosis. We previously reported the technique in the "journal of thoracic disease". However, I accepted your suggestions, provided citation, and revised the manuscript. In the expansion technique, we expanded the level of sympathicotomy to levels ranging from R5 to R12 by chain ablation to prevent compensatory while avoiding injury to the splanchnic nerves.

Changes in the text: Thanks for your comments. I more detailed the surgical techniques like abstract.

Changes in the text: All subjects underwent bilateral endoscopic sympathicotomy with or without the expansion of sympathicotomy. T2 and T3 sympathicotomy were routinely performed in patients with craniofacial and palmar hyperhidrosis, respectively. In the expansion sympathicotomy, we expanded the level of sympathicotomy to levels ranging from R5 to R12 by chain ablation to prevent compensatory while avoiding injury to the splanchnic nerves. (line 17-21 at page 8)

Comment 4: Page 12, line 5 and line 11- The acronym CA is cited. She has not been previously described. It could be presented on page 9, line 5 "... was evaluated based on AUC , accuracy (CA)..."

Reply4: CA means the classification accuracy. I changed CA into accuracy to avoid confusion.

Changes in the text: 0.961 accuracy (line 23 at page 12)

Comment 5: Page 4, lines 16, 18 and 19- In the abstract some data are presented in decimals and others in percentages, in the article, all are presented in decimals (Page 12, lines 5, 11 and 12). Suggestion would be to present it in the same way.

Reply 5: Thanks for your comments. I revised the manuscript as your suggestions. We presented all in decimals.

Changes in the text: an 0.961 accuracy, 0.961 F1 score, 0.961 precision, 0.961 Recall, and 0.972 area under the curve (AUC) for classification of hyperhidrosis type. The random forest model with five-fold cross validation outperformed showed an 0.852 accuracy, 0.853 F1 score, 0.856 precision, 0.852 Recall, and 0.914 AUC (line 16-19 at page 4)

Comment 6: Page 7, line 12- Was the telephone survey performed for all patients included in the study? Were the data used on the improvement of symptoms and the degree of HC from July 2022 or from 1 month after surgery (line 19)? At 1 month after surgery, the perception of HC may be different years after surgery.

Reply 6: I am sorry for my mistyping again. The study period was "From March 2017 to December 2021". I revised the manuscript as the reply 1. Therefore, the period after surgery was over at least 6 months.

Changes in the text: From March 2017 to December 2021... (line 18 in page 3)

Comment 7. : Page 10, line 8- 46 craniofacial + 86 palmar were included, totaling 132 patients. If the patient total is 128, 4 patients have both types of hyperhidrosis? The same problem occurs in Figure 1. - Page 19: table 1. The total number of the palm type is 82, but on page 10, line 8 it was 86. What is the correct number? - Page 20, table 2- put the total number of patients with craniofacial type and palmar type.- Page 21, table 3- put the total number of failure (n=5) and success (n=123). - Page 22, table 4- put the total number of low degree (n=93) and high degree (n=35).

Reply 7: Thanks for comments on the important issue. 4 patients had both craniofacial and palmar hyperhidrosis. Hyperhidrosis involving craniofacial area was regarded as craniofacial type Therefore, I should have corrected the number of palmar type as 82 instead of 86 in order to avoid confusion. I revised this error. However, the other numbers are all correct.

Changes in the text: palmar type 82, (figure 1, line 6 at page 11)

Reviewer B

The paper is well structured and narrated. However, there are some issues that should be resolved/addressed in order to improve the manuscript for its publication.

Comment 1: Introduction:

-Regarding introduction, the authors should state the primary objective or aim of the study more clearly.

Reply 1: Thanks for your comments. I revised the primary aims more clearly as your suggestions.

Changes in the text: The aims of the present study are to investigate the characteristics of primary hyperhidrosis and to predict the degree of CH using HRV findings and basic clinical data.(line 21-23 at page 7)

Comment 2: -Page 6, Line 13-14: The message in this line is very similar to line 19-20. I recommend to structure it better.

Reply 2. Thanks for your comments. I removed the sentence in line 19-20 as your recommends.

Changes in the text: I removed the sentence in line 19-20 at page 6

Comment 3: Methods:

-Regarding statistics, if authors state how they present continuous variables (mean and sd) they should also state how categorical variables are presented.

Reply 3. Thanks for your comments. Categorical variables are presented by number in the group. Of course, number was shown in the table.

Changes in the text: Categorical variables are presented by number in the group (line 22-23 at page 9)

Comment 4: Results

-Page 10, Line 7. The authors state that "...and patients were divided into 2 by the mean age". I suggest that this could be better explained in a separate sentence.

Reply 4: Thanks for your comments. I revised the manuscript as your comments.

Changes in the text: The mean age of study subjects at sympatricotomy was 30.1 years (± 16.7). Subjects were divided into two by the mean age (line 3-4 at page 11)

Comment 5: Page 11, line 13. The authors should show the percentage of patients who develop CH in the craniofacial type and in palmar type, not only absolute frequency.

Reply 5. Thanks for your comments. I added the percentage of patients who develop CH in the craniofacial type and in palmar type.

Changes in the text: I added the percentage of patients (in table 1-4, line 4-9 at page 11)

Comment 6: -Page 11, line 16. The authors state that: “Univariate analysis showed RMSSD and autonomic nervous system predominance based on HRV parameters were associated with developing CH.” They must show results of the univariate analysis by means of an odds ratio in a table or in the text to understand the association and see its significance. I can’t find that in the results, they only showed the results of the multivariate analyses.

Reply 6: Thanks for your comments. I showed the results in the table 4. Table 4 shows RMSSD ($p=0.047$) and autonomic nervous system predominance ($p=0.006$) based on HRV parameters were associated with developing CH.

Changes in the text: see table 4.

Comment 7: -Page 11, line 17. I also can’t find data to conclude this in the results or in the tables. You must show data to support this fact.

Reply 7: Univariate analysis shown in the table 4 shows that RMSSD ($p=0.047$) and autonomic nervous system predominance ($p=0.006$) based on HRV parameters were associated with developing CH.

Changes in the text: see table 4.

Comment 8: -Along results, authors should report categorical variables in frequency and percentages.

Reply 8 :Thanks for your comments. I added frequency and percentages in categorical variables as your comments.

Changes in the text: I added the percentage of patients (in table 1-4, line 4-9 at page 11)

Comment 9: Discussion

The authors could improve the discussion by explaining more about the machine learning results and why they conclude their algorithms can predict CH.

Reply 9: Thanks for your comments. We presented the performance score of the models to conclude our models can predict CH.

Changes in the text: In the present study, the model performance for type classification were 0.972 AUC, 0.961 accuracy, 0.961 F1 score, 0.961 precision, and 0.961 recall. In addition, the model performance for CH prediction were 0.914 AUC, 0.852 accuracy, 0.853 F1 score, 0.856 precision, and 0.852 recall (line 15-17 at page 14)

Comment 10: Tables: Table 1

I suggest that it is not necessary to report again that the continuous variables are expressed mean \pm SD. The authors should add percentages in categorical variables.

Reply 10: Thanks for comments. As mentioned above, we added percentages in categorical variables.

Changes in the text: I added the percentage of patients (in table 1-4, line 4-9 at page 11)

Comment 11: Table 2,3,4 The authors should add the total of subjects in each column as they did in table1. The authors should add percentages in categorical variables.

Reply 11: Thanks for comments. I revised the tables as your comments.

Changes in the text: I added the total of subjects in each column and the percentage of patients (in table 1-4, line 4-9 at page 11)

Comment 12: Minor issues:

Page 3 line 8: I recommend adding a percentage to illustrate better how infrequently it is.

Reply 12: I revised the manuscript as your comments. I added percentages in categorical variables

Changes in the text: I added the total of subjects in each column and the percentage of patients (in table 1-4, line 4-9 at page 11).

Comment 13: Page 3 Line 23: Suggested edit: Data collected...

Reply 13: We edited that as your comments.

Changes in the text: Data also collected age (line 23 at page 3)

Comments 14: Page 11 line 12: Suggested edit: Low and high degree of CH were observed in 93 and 35 subjects, respectively.

Reply 14: I edited that as your comments.

Changes in the text: Low and high degree of CH were observed in 93 (72.7%) and 35 (27.3%) subjects, respectively (line 9 at page 11).

Comment 15: Page 11 line 13: Suggested edit: CH after sympathicotomy was developed more often in...

Reply 15 I edited that as your comments.

Changes in the text: High-degree CH after sympathicotomy was developed more often in the craniofacial type ($p < 0.001$). (line 5-6 at page 12)

Comment 16:

Page 13: I suggest to replace the word however in some cases at discussion, it appears so often.

Reply 16: I removed the word if possible.

Changes in the text: I removed some of "however" (page 13-14)

Comment 17: Page 13, line 22: Suggested edit: yielded excellent results, which could be useful...

Reply 17: I edited the sentence as your comments.

Changes in the text: The classification model for hyperhidrosis type and the prediction model for CH after sympathicotomy yielded excellent results, which could be useful in clinical practice (line 18-19 at page 14)

Comment 18: Page 14, line 24, typo error, there is a dot after however.

Reply: 18: Thanks for your comments. I corrected this error as your comments.

Changes in the text: a dot was removed.

Reviewer C

Comment 1: First, I would like to say congratulations for all the authors for the work and the innovation to bring the machine learn in the thoracic surgery scene.

The title and the abstract are good. It is interesting to mention in the summary results the type of hyperhidrosis that was most associated with HC.

The introduction is clear. It would be good if the authors explained a little more about the rates of compensatory sweating after sympathectomy, since the studies present very different rates and, many, show that the quality of life after surgery improves, despite the compensatory sweating. This is an important point and must be considered due to the variability of cases presented in the literature.

Reply1: Thanks for your kind comments. I mentioned the rates of compensatory sweating after sympathectomy as your comments.

Changes in the text: Incidence of CH varies among centers, up to 98% although surgical techniques advances. (line 8 at page 7)

Comment 2: Materials and methods

The study population is clearly presented, and the inclusion criteria are adequately informed. It is important to mention how the data obtained in the telephone survey were collected (standard instrument?) and how satisfaction and HC were evaluated at this stage. Was a questionnaire used? This is important because the way the question is asked can be biased.

Reply 2. Thanks for your raising basic issues. We used a questionnaire including symptom improvement, recurrence, degree of CH, and overall satisfaction after sympathicotomy. I mentioned it in the manuscript as your comments.

Changes in the text: The telephone survey using a questionnaire was conduct in July 2022 and included symptom improvement, recurrence, degree of CH, and overall satisfaction after sympathicotomy (line 12-14 at page 8).

Comment 3: The HRV test and its variables are well described.

Statistical analysis is well described and justified. A point that draws attention was the measure of effect used

in the multivariate analysis. Since the design does not include a control group (all patients underwent sympathectomy), this is not a case-control study, but a retrospective cohort study. Thus, it is more appropriate to use relative risk (RR) as an effect measure.

Reply 3. Thanks for your comments. I agreed with you (this is not a case-control study, but a retrospective cohort study), I corrected this as your recommendations.

Changes in the text: table 5

Comment 4: Results

The descriptive analysis is well done, and Table 1 summarizes the data very well. Since the presence of HC is more expected in craniofacial hyperhidrosis, it is interesting that all results (HRV before and after sympathectomy) are presented separately for each type of hyperhidrosis. The text and table 3 bring the results together, which does not favor the discussion of the data.

Reply 4: Thanks for your comments. I am afraid I do not understand your comments. Symptom improvement after sympathectomy did not differ based on the type and failure of sympathectomy occurred in the extremely small number of cases (n=5). Therefore, improvement of sweating (HRV before and after sympathectomy) could not be presented separately for each type of hyperhidrosis.

Changes in the text: line 8 at page 11

Comment 5: The authors justify the choices of covariates included in the multivariate analysis (8 in total), but present in the text only those with significance and in Table 5 only 4. It is important to bring all the results found, since BMI values, gender and type of hyperhidrosis are relevant factors in clinical practice.

Reply 5: Thanks for your comments. Age group, sex, BMI, expansion of sympathectomy, hyperhidrosis type, RMSSD, and autonomic nervous system predominance were included as covariates in multivariate analysis which was performed using a binary logistic regression test (backward method). The only last step (step 4th) of statistical calculations showed this table, and the other covariates were removed step by step. I think these covariates were influenced by HRV parameters.

Changes in the text: table 5

Comment 6: Analyzing table 5, I expected to find a higher risk of HC in the craniofacial hyperhidrosis group, but this data is not included in the table, it is only mentioned in the text.

Reply 6: I am afraid I do not understand. Table 5 shows that palmar type is an influencing factor (p=0.001), which means a higher risk of HC in the craniofacial hyperhidrosis group.

Changes in the text: table 5

Comment 7: Discussion As this is the first article to use machine learning in hyperhidrosis, the authors could present counterpoints from the literature and the data found in the study. I also expected a discussion about the influence of palmar hyperhidrosis on HC at the expense of craniofacial hyperhidrosis, something that is not seen in the literature. As it stands, the discussion feels more like an extension of the introduction.

Reply 7: Thanks for your comments. I am afraid I do not understand. In the present study, the main aim is to adopt machine learning analysis for prediction of CH and classification of the types using HRV. The influence of palmar hyperhidrosis on CH is also analyzed in this present study.

Changes in the text: figure 2-3, table 5

Comment 8: A very important point is the presentation of the limitations of the study, which is in line with what was proposed by STROBE.

Reply 8. Thanks for your comments. I presented the limitations of this study in the last paragraph in the discussion.

Changes in the text: line 24-25 at page 14 and line 1-4 at 15 page)

Reviewer D

Comments 1: Interesting manuscript, that tries to tackle the question which patients benefit from sympathectomy and which are better left untreated, using HRV pre-operatively to predict postoperative CH. While an algorithm to predict CH is found, it would be nice however if this leads to a more concrete and clinically usable advice. Can the authors produce means, or advice for other clinicians to use the lessons

learned? Furthermore, i feel the term 'expansion of sympathicotomy' has to be elaborated.

Reply 1. Thanks for your warm comments. This study is the first to adopt machine learning algorithms in primary hyperhidrosis and further study should be required to leads to a more concrete and clinically usable advice as your comments. I hope to develop this algorithm and share it with others. The study on the “expansion of sympathicotomy” was published in the JTD and I explain it more detailly as your recommendations.

Changes in the text: This machine learning algorithm may be convenient and useful for selecting treatment modality and improvement of sympathicotomy outcomes. (line 14-15 at page 15)