

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Is the Yale Global Tic Severity Scale a valid tool for parent-reported assessment in the pediatric population? A prospective observational study in Taiwan
<b>AUTHORS</b>	Ho, Che-Sheng; Huang, Jia-Yun; Yang, Chien-Hui; Lin, Yi-Jie; Huang, Ming-Yuan; Su, Yung-Cheng

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Andrea E. Cavanna BSMHFT and University of Birmingham
<b>REVIEW RETURNED</b>	23-Oct-2019

<b>GENERAL COMMENTS</b>	<p>Ref: bmjopen-2019-034634 Title: Yale Global Tic Severity Scale is a Valid Tool for Self-reported Assessment in the Pediatric Population: A Prospective Observational Study</p> <p>Thank you for the opportunity to review this paper and offer my comments on it. I enjoyed reading this interesting manuscript, in which the authors present the results of an original study aimed at determining whether the Yale Global Tic Severity Scale (YGTSS) is a valid tool for self-reporting in the population of patients with Tourette syndrome. A total of 594 patients were enrolled in this study, and 3356 evaluations were contributed by their guardians. On average, each participant contributed 5.65 self-reported YGTSS evaluations during the study period. The results showed that the self-reported YGTSS is a promising tool for the assessment of tic severity in patients with Tourette syndrome, as it demonstrated good discriminative ability for disease severity, with user precision increasing with experience.</p> <p>The research question is clinically important. The title and abstract are informative and give a clear idea of what to expect from the text. This article is methodologically sound and clearly written. The main limitations have been adequately addressed in the Discussion section.</p> <p>I have only a minor comment, which the authors might want to consider in order to improve the overall quality of their manuscript: - It would be helpful to provide an English translation of the text included in Figure 1, in consideration of the wider readership of the journal.</p>
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<b>REVIEWER</b>	Kyriazi Maria Aristotle University of Thessaloniki, Greece
<b>REVIEW RETURNED</b>	17-Nov-2019

<b>GENERAL COMMENTS</b>	The research question to assess YGTSS as a valid tool for self-reported assessment in the pediatric population is well addressed and justified by the results and is on a subject that will fill a gap in the literature for this field.
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<b>REVIEWER</b>	Dr. Molly Colvin Massachusetts General Hospital Harvard Medical School United States
<b>REVIEW RETURNED</b>	02-Feb-2020

<b>GENERAL COMMENTS</b>	<p>Using the YGTSS as a parent-report and web-based measure of tic severity is an interesting idea. From a clinical perspective, having more frequent and quantitative data about tic severity would likely improve treatment outcomes and help improve communication between families and their providers. The authors are to be commended in collecting as much data as is reported in this study.</p> <p>As described, the study has several major limitations:</p> <p>The literature review is incomplete; the authors do not discuss other standardized measures that have been designed for parents to rate their child's tics. A review of these was published in <i>Movement Disorders</i> in 2017 (Martino, et al). Also in the abstract, the authors say that the YGTSS is "time consuming and requires a highly trained, experienced interviewer to ensure accurate and reliable use of the assessment, making its use in a busy clinical setting unfeasible" (p 3). This statement seems to contraindicate the entire premise of the study, which is to show that the YGTSS can be used reliably by parents.</p> <p>There are also flaws in research design that potentially limit the study's validity. First, parents always completed the YGTSS the day before the pediatric fellow completed it, raising concerns about an order effect (i.e., the parent will give the same answers two days in a row). Second, only 1455/3356 parent evaluations were paired with a simultaneous evaluation by a pediatric fellow. I assume that the reason for this difference is that pediatric fellow evaluations were performed when possible and not systematically, but this is unclear. Also unclear is whether this would account for the attrition between the total number of patients included in the sample (594) and the number in the final analysis (527). Regardless, this raises the likelihood of sampling bias. Third, there is no means of checking that parents had achieved an acceptable level of fidelity in use of the YGTSS after the neurologist explained it to them. Similarly, pediatric fellows (who may or may not have expertise in tic disorders) were "taken as the expert standard" but there is no mention of their training or whether they had demonstrated reliability, including inter-rater reliability, with the YGTSS. The impact of patient characteristics (e.g., severity of tics, duration since initial diagnosis) is also not addressed, except to say that "we were unable to perform</p>
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	<p>subgroup analyses for patients with newly diagnosed TS" (p. 10) but there was no explanation as to why this would not be possible.</p> <p>The statistical analysis is insufficiently explained, specifically with regard to the generalized estimate equation method. The authors also note that "our sample size in this study is large enough that insufficient power was not an issue" (p. 9) but the power analysis was not reported. The authors also state that "internal reliability may be difficult to be evaluated between the participants" (p. 10) but it is not clear why this would be the case.</p> <p>The authors note that the study was approved by the local IRB but also report that patients were not involved. In reality, patients were involved as parents and clinicians were assessing, directly or indirectly, the patients' tics to complete the questionnaire.</p> <p>As far as I know, Dr. James Leckman retains the copyright to the YGTSS. The authors should state how the Google forms document does not infringe on copyright and whether their Chinese version has been approved for use.</p> <p>Finally, the authors do not discuss what might account for the change in parent reported scores over time, with greater alignment to the clinician's over time. Assuming that this does not reflect communication between providers and parents regarding YGTSS scores as part of clinical care, this might suggest that parents are becoming more practiced and like clinicians over time? It would be nice if this mirrored a pattern seen in the neurology fellows when they first start using the YGTSS.</p> <p>Minor Issues:</p> <ul style="list-style-type: none"> <li>- The title is misleading. I would recommend changing "self reported" to "parent reported" as the patients were not involved in rating their tics.</li> <li>- There are a few minor errors in English language to be corrected before publication (e.g., Figure 2).</li> <li>- I am unable to confirm that Figure 1 is the YGTSS because it is in Chinese.</li> </ul>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

1. It would be helpful to provide an English translation of the text included in Figure 1, in consideration of the wider readership of the journal.

Reply:

1. We appreciate the reviewer's comments and have added an English translation of the text included in Figure 1.

Reviewer: 2

The research question to assess YGTSS as a valid tool for self-reported assessment in the pediatric population is well addressed and justified by the results and is on a subject that will fill a gap in the literature for this field.

Reply:

We appreciate the reviewer's recommendations.

Reviewer: 3

1. The literature review is incomplete; the authors do not discuss other standardized measures that have been designed for parents to rate their child's tics. A review of these was published in *Movement Disorders* in 2017 (Martino, et al).
2. Also in the abstract, the authors say that the YGTSS is "time consuming and requires a highly trained, experienced interviewer to ensure accurate and reliable use of the assessment, making its use in a busy clinical setting unfeasible" (p 3). This statement seems to contraindicate the entire premise of the study, which is to show that the YGTSS can be used reliably by parents.
3. There are also flaws in research design that potentially limit the study's validity. First, parents always completed the YGTSS the day before the pediatric fellow completed it, raising concerns about an order effect (i.e., the parent will give the same answers two days in a row).
4. Second, only 1455/3356 parent evaluations were paired with a simultaneous evaluation by a pediatric fellow. I assume that the reason for this difference is that pediatric fellow evaluations were performed when possible and not systematically, but this is unclear. Also unclear is whether this would account for the attrition between the total number of patients included in the sample (594) and the number in the final analysis (527). Regardless, this raises the likelihood of sampling bias.
5. Third, there is no means of checking that parents had achieved an acceptable level of fidelity in use of the YGTSS after the neurologist explained it to them. Similarly, pediatric fellows (who may or may not have expertise in tic disorders) were "taken as the expert standard" but there is no mention of their training or whether they had demonstrated reliability, including inter-rater reliability, with the YGTSS.
6. The impact of patient characteristics (e.g., severity of tics, duration since initial diagnosis) is also not addressed, except to say that "we were unable to perform subgroup analyses for patients with newly diagnosed TS" (p. 10) but there was no explanation as to why this would not be possible.
7. The statistical analysis is insufficiently explained, specifically with regard to the generalized estimate equation method.
8. The authors also note that "our sample size in this study is large enough that insufficient power was not an issue" (p. 9) but the power analysis was not reported.
9. The authors also state that "internal reliability may be difficult to be evaluated between the participants" (p. 10) but it is not clear why this would be the case.
10. The authors note that the study was approved by the local IRB but also report that patients were not involved. In reality, patients were involved as parents and clinicians were assessing, directly or indirectly, the patients' tics to complete the questionnaire.
11. As far as I know, Dr. James Leckman retains the copyright to the YGTSS. The authors should state how the Google forms document does not infringe on copyright and whether their Chinese version has been approved for use.
12. Finally, the authors do not discuss what might account for the change in parent reported scores over time, with greater alignment to the clinician's over time. Assuming that this does not reflect communication between providers and parents regarding YGTSS scores as part of clinical care, this might suggest that parents are becoming more practiced and like clinicians over time? It would be nice if this mirrored a pattern seen in the neurology fellows when they first start using the YGTSS.
13. Minor Issues: The title is misleading. I would recommend changing "self reported" to "parent reported" as the patients were not involved in rating their tics.
14. There are a few minor errors in English language to be corrected before publication (e.g., Figure 2).
15. I am unable to confirm that Figure 1 is the YGTSS because it is in Chinese.

Reply:

1. We appreciate the reviewer's comments and have revised the introduction part. Several self-report instruments for TS have been developed for this purpose. The Proxy Report Questionnaire for Parents and Teachers and the Apter 4-questions are limited by insufficient validation and relatively

low specificity. The Premonitory Urges for Tics Scale has shown good psychometric properties. However, its use is not acceptable for patients younger than 10 years.

2. We appreciate the reviewer's comment and revised this part.

3. We appreciate the reviewer's comments. We assumed that order effects refer to differences in participants' responses that result from the order. However, it is actually part of our study results that the difference between the participant and physician scores decreased as the number of times the parent-evaluation was performed increased. Order effects should not be a concern in our study.

4. We are sorry for the confusion. On the date of the visit, a pediatric neurology fellow was assigned to the patient by convenience sampling in the waiting room and also administered the YGTSS. Not every patient in the waiting room will receive the evaluation, resulting in the differences in numbers. Some patients may not be evaluated under this circumstance. We have addressed this part in the limitation part. The pediatric fellows visit and evaluate the patients in the waiting room by convenience sampling, which may lead to sampling bias.

5. We appreciate the reviewer's comments and have revised the limitation. It is also difficult to train many parents repeatedly to ensure them to achieve an acceptable level before they posted their scores, and the internal reliability may be difficult to be evaluated. There may also be variability in the evaluation of the YGTSS among pediatric fellows.

6. We appreciate the reviewer's comments and have revised the limitation. In our cohort there are only a few patients with newly diagnosed TS. As a result, we were unable to perform subgroup analyses for these patients. We also did not adjust for important patient characteristics such as severity of tics and duration since initial diagnosis because of lack of information.

7. We are sorry for the confusion and have added more illustration. Linear regression was used to evaluate differences of scores among participants and pediatric fellows. To adjust the correlated data from multiple evaluations by the same participants, the generalized estimate equation method was adapted to account for clustering of participants in the evaluation of score differences.

8. We are sorry for the confusion. Because of overall good ability to discriminate a mild TS attack via parent-reporting, we assumed there is no type 2 error in our study and insufficient power was not an issue. We will remove this part from the discussion.

9. We are sorry for the confusion and have revised the limitation. As more than 500 patients are included in the database, it is difficult to train so many parents repeatedly to ensure them to achieve an acceptable level in use of the YGTSS before they evaluate their children, and the internal reliability may be difficult to be evaluated between the participants.

10. We appreciate the reviewer's comment and have revised the ethic statements.

11. We appreciate the reviewer's concern. Our first author has emailed Prof. James Leckman for the permission of translation. We have attached the email as the supplement.

12. We appreciate the reviewer's comment and have revised the discussion part. Another reason for our positive results is that the participants were aware of the disease and highly motivated to be involved in the TS management. They may be more likely to present precise evaluations if possible. During the multiple interactions about the conditions with their clinicians, participants may become more practiced over time. We are lack of information if this mirrored a pattern seen in the neurology fellows when they first start using the YGTSS.

13. We have revised the title as "Is Yale Global Tic Severity Scale a Valid Tool for Parent-reported Assessment in the Pediatric Population? A Prospective Cohort Study" based on the reviewer's suggestion.

14. We appreciate the reviewer's comments and have revise the figure. Our manuscript has been edited by a professional medical editor who is a native English speaker. We have attached the certification.

15. We appreciate the reviewer's comments and have added an English translation of the text included in Figure 1.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Andrea E. Cavanna BSMHFT and University of Birmingham, United Kingdom
<b>REVIEW RETURNED</b>	08-Mar-2020

<b>GENERAL COMMENTS</b>	The authors have satisfactorily addressed the reviewer's comments.
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<b>REVIEWER</b>	Dr. Molly Colvin Massachusetts General Hospital Harvard Medical School United States
<b>REVIEW RETURNED</b>	13-Mar-2020

<b>GENERAL COMMENTS</b>	<p>I appreciate that the authors have made substantial revisions to the manuscript that have greatly improved its clarity and present a more balanced perspective of strengths and weaknesses. Unfortunately, I don't think that the revisions are sufficient for publication at this time, although I am optimistic that the remaining concerns can be addressed. 1) The inclusion and repetition of the statement that the YGTSS is "relatively time consuming and requires a highly trained, experienced interview to ensure accurate and reliable use of the assessment" continues to contradict the entire premise (i.e., that parents can do it easily and reliably). 2) It also remains unclear whether the authors have retained Dr. Leckman's permission to use the YGTSS in the manner described. I see the email to Dr. Leckman but there isn't a reply. 3) Also missing are the Figures from the first draft and I was hoping that Figure 2 would be revised to make it clearer what data is included in the final dataset. 4) I am still not entirely clear with the statistical procedures that were used and would recommend consultation with a statistical expert. 5) In this abstract, I see the results for patients with "mild tic attacks" but not for more severe attacks. If these concerns can be addressed and there is confirmation of Figure 1 (which is in Chinese), then I think the paper would make a nice addition to the literature. As I noted in my earlier review, having more frequent and quantitative parent data about tic severity would likely improve clinical treatment and communication between families and providers.</p>
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## VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

The authors have satisfactorily addressed the reviewer's comments.

Reply:

We appreciate the reviewer's comments.

Reviewer: 3

1. The inclusion and repetition of the statement that the YGTSS is "relatively time consuming and requires a highly trained, experienced interview to ensure accurate and reliable use of the assessment" continues to contradict the entire premise (i.e., that parents can do it easily and reliably).
2. It also remains unclear whether the authors have retained Dr. Leckman's permission to use the YGTSS in the manner described. I see the email to Dr. Leckman but there isn't a reply.
3. Also missing are the Figures from the first draft and I was hoping that Figure 2 would be revised to make it clearer what data is included in the final dataset.
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5. In this abstract, I see the results for patients with "mild tic attacks" but not for more severe attacks. If these concerns can be addressed and there is confirmation of Figure 1 (which is in Chinese), then I think the paper would make a nice addition to the literature. As I noted in my earlier review, having more frequent and quantitative parent data about tic severity would likely improve clinical treatment and communication between families and providers.

Reply:

1. We appreciate the reviewer's comments and have removed this part to avoid confusion.
2. We appreciate the reviewer's concern. We have contacted Dr. Leckman again and have attached the email regarding the permission.
3. We appreciate the reviewer's comments. We have added an English translation of the text included in Figure 1 in the last revision. We have revised the Figure 2 to make the included data clearer.
4. We appreciate the reviewer's comments and have collaborated with our statistician to revise the statistical part. We first evaluated the absolute differences in the YGTSS scores by subtracting the scores of parents from that of physicians, and the results are summarized in Table 1. We also assessed the difference between the two measurements across multiple visits using linear regression. To adjust for correlations in the data due to being collected at multiple times by the same participants, the generalized estimating equation (GEE) method was adapted to account for clustering of participants in the evaluation of score differences.

We also dichotomized tic attack as mild or moderate/severe by defining a mild attack as a YGTSS score  $<20$  and a moderate to severe tic attack as  $>20$ . The discriminatory power of the parent-reported YGTSS for a moderate to severe attack was assessed by using the area under the receiver operating characteristic curve (AUROC) based on a logistic regression model with GEE.

5. We appreciate the reviewer's comments and have revised this part. Since we divided our parent data into two groups (mild tic attack versus moderate to severe tic attack), the AUROC is identical when we change our diagnostic interest to moderate to severe tic attack. The sensitivity of identifying patients with mild tic attack will become the specificity of identifying patients with moderate to severe tic attack and vice versa.

**VERSION 3 - REVIEW**

<b>REVIEWER</b>	Molly Colvin, PhD Massachusetts General Hospital Harvard Medical School Boston, MA USA
<b>REVIEW RETURNED</b>	05-Jun-2020

<b>GENERAL COMMENTS</b>	The paper is substantially improved from prior versions. The authors have addressed the major methodological limitations in the discussion section. Results are more clearly described and presented.
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