

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Association between multiple symptoms and Quality of Life of pediatric cancer patients in Brazil - a cross-sectional study.
<b>AUTHORS</b>	Cadamuro, Sandra; Franco, Julia; Paiva, Carlos; Oliveira, Marco; Paiva, Bianca

## VERSION 1 – REVIEW

<b>REVIEWER</b>	Mohammad Gamal Sehlo Professor of psychiatry, Zagazig University, Zagazig, Egypt.
<b>REVIEW RETURNED</b>	05-Dec-2019

<b>GENERAL COMMENTS</b>	<p>Dear, Dr. Edward Sucksmith BMJ Open Managing Editor</p> <p>This is my final report about the revision of Manuscript ID bmjopen-2019-035844 entitled "Influence of multiple symptoms on the quality of life of pediatric cancer patients: a cross sectional study" for BMJ Open.</p> <p>There are several drawbacks in this study</p> <p>1) The abstract :</p> <p><b>Primary outcome measures (page 2, in line 10 ) :</b></p> <p>The sentence should be To evaluate the most prevalent symptoms and it's influence on quality of life in pediatric cancer patients.</p> <p><b>Under the results in the abstract (page 2, line 12 ) :</b></p> <p>The results are totally corrupted and do not reflect the main results of the paper at all , so it must be rewritten again to reflect exactly the results of the paper in a brief manner</p> <p>2) <b>Under Strengths and limitations of this study ( page 2, line 25) :</b></p> <p>The authors must add under the limitations that they did not assess the psychological factors that may influence the quality of life more than the physical factors</p> <p>3) <b>The introduction :</b></p>
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	<p>1) The authors did not mention clearly the importance of the study at the end of the introduction , what this research will add to the literature, as the previous studies found clearly that the symptoms of pediatric cancer are associated with lower quality of life , which is nearly the same results of this study so what this study adds .</p> <p>2) The authors did not mention studies that are held in the locality of the study which are important to be mentioned</p> <p><b>4) The results :</b></p> <p>1) The sentence with an association with time since diagnosis for the proxy-reported version ( page 9, lines 6,7) should be deleted.</p> <p>2) Under Relationship between the PedsQL and SSPedi-BR symptoms</p> <p>The sentence , ( page 10 , lines 1-3) The symptoms “Feeling tired”, “Throwing up or feeling like you may throw up” and “Constipation” were statistically related to the four domains: emotional, school functioning, physical and social (table 4) . While in reviewing table 4, all the symptoms that are screened by SSPedi-BR symptoms affect negatively PedsQL except changes in taste and diarrhea ( why all these affecting symptoms are not included in the paragraph)</p> <p>Also the sentence Regarding the proxy-reported version, only the emotional domain showed a relationship with symptoms on the SSPedi-BR scale: "Feeling scared or worried (concerned)" (p=0.001), "Feeling more or less hungry (don't feel like eating) than you usually do" (p=0.048) and "Changes in taste (flavor of food)" (p=0.031). (page 10 , lines 4-7) , where is the table that reflecting these results</p> <p><b>5) Discussion :</b></p> <p>The discussion needs to be more deep to highlight the importance of the results</p>
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<b>REVIEWER</b>	Carsten Müller University of Münster, University Sports
<b>REVIEW RETURNED</b>	University of Münster, University Sports 18-Dec-2019

<b>GENERAL COMMENTS</b>	<p>The manuscript entitled „Influence of multiple symptoms on the quality of life of pediatric cancer patients: a cross sectional study” represents a cross-sectional study examining the impact of numbers and severity of symptoms, assessed using the Symptoms Screening in Pediatrics Tool, on quality of life, assessed using the Pediatric Quality of Life Inventory (PedsQL) in pediatric oncology.</p> <p>Generally, the paper would benefit from reviewing of a native speaker/ language editing services. Although the study design and outcome variables seem appropriate, the manuscript would also benefit from a clarification of the objectives / primary outcome measures and statistical analyses.</p> <p><b>MAJOR:</b></p>
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	<p>The title "Influence of multiple symptoms on quality of life..." suggests a cause-effect-relationship that cannot be assessed in a cross-sectional study. I would propose to rephrase the title to "Association of symptoms, quality of life, and clinical characteristics in pediatric cancer patients – a cross sectional study"</p> <p>Abstract, page 2, ll. 10-11: Bearing in mind that the objectives of the study were to evaluate the influence of multiple symptoms on quality of life (QoL), the primary outcome measure (dependent variable) is QoL (PedsQL), and the secondary outcome measures should be symptoms (SSPedi-Br). However, in this case, larger parts of the manuscript had to be rewritten, focusing on QoL in pediatric cancer patients and the dependency of QoL on the number of symptoms and symptom severity. As mentioned above and in order to do justice to the actual objective of the paper, I would suggest to focus on the associations of the outcomes (QoL and symptoms) and their association with clinical characteristics.</p> <p>Statistical analysis: What is the reason for using Mann-Whitney tests to compare the various clinical characteristics and PedsQL scores, instead of using MANOVA models? E.g., in case that data lacked normal distribution, median and IQR should be presented (tables 3 and 4). Moreover, information on p-value adjustments due to alpha error accumulation following multiple testing are missing. This most likely will have implications on the interpretation and discussion of the results. Please also consider calculating effect sizes.</p> <p><b>MODERATE:</b> Please provide information on the psychometric properties of the questionnaires used.</p> <p><b>MINOR:</b> Abstract, page 2, ll. 8-9: exclusion criteria: please indicate how many patients and proxies had neuropsychiatric disorders and/or visual impairment (N=)</p> <p>Abstract, page 2, ll. 13-15: "... between the time of diagnosis and surgical procedure [on symptom severity]." For clarification purposes, please the text in brackets [...].</p> <p>Table 1: The authors refer to the educational level of the patients – however, no information on assessment of the educational level have been provided in the methods' section. Please clarify.</p> <p>Please make consistent use of the PedsQL throughout the manuscript, because there are at least four different spellings.</p> <p>Page 4, l. 9: Please consider rephrasing "objective" in connection with self-reports. Maybe "valid" and/or "reliable" fits better?</p> <p>Conclusion: page 12, ll. 15-17: it says "The present study shows that pediatric patients experienced a higher prevalence of symptoms during treatment ..." It is unclear to whom the authors refer. A higher prevalence of symptoms compared to...? "and that quality of life in the social emotional domain was negatively and significantly influenced" Again, during treatment refers to "time of diagnostic"? or "inpatient vs. outpatient clinic"? Please clarify.</p>
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## VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Mohammad Gamal Sehlo

Institution and Country: Professor of psychiatry, Zagazig University, Zagazig, Egypt.

Please state any competing interests or state 'None declared': None declared

The paper needs major revision by the authors and to focus on and be adherent to their results to highlight the importance of their results in the abstract, section of results and discussion. the study is not focusing well on results in writing so it is confusing and distracting to the reader

Response:

We would like to thank Mr. Sehlo for his in depth review and comments. A complete analysis of several of the different sections of this paper was conducted. Deviation from highlighting the results of the study or areas that proved to be confusing or distracting have been rewritten in order to provide a better comprehension.

1) The abstract :

Primary outcome measures (page 2, in line 10 ) :

The sentence should be To evaluate the most prevalent symptoms and it's influence on quality of life in pediatric cancer patients.

Response: We agree that the statement needed to reflect more on what the study sought out to achieve. We thank the reviewer for suggesting a clearer sentence. The sentence now reads as follows:

"To evaluate the most prevalent symptoms and clinical characteristics, and their influence on the QoL in Brazilian pediatric cancer patients".

Under the results in the abstract (page 2, line 12 ) :

The results are totally corrupted and do not reflect the main results of the paper at all , so it must be rewritten again to reflect exactly the results of the paper in a brief manner

Response:

We agree with Mr. Sehlo, the results in the abstract section of the paper definitely need to be rewritten. We thank you for your suggestion. The results section in the abstract now reads as follows:

"The analysis of SSPedi-BR identified the prevalent symptoms presented in all participants that had an effect on QoL. This test also evaluated the degree of severity of the symptoms in relation to time since diagnosis. A significantly higher level of severity of symptoms was identified by proxies presented in non-surgical patients at less than six months of diagnosis. These patients have a greater probability of presenting severe symptoms. An analysis of the clinical characteristics associated with PedsQLTM demonstrated no significant effect on QoL.

When examining the association between the findings of SSPedi-BR and PedsQLTM a significant negative influence on the QoL was observed in the symptom of "feeling tired", which had an effect on all four domains of QoL".

2) Under Strengths and limitations of this study ( page 2, line 25) :

The authors must add under the limitations that they did not assess the psychological factors that may influence the quality of life more than the physical factors

Response:

We appreciate Mr. Sehlo's suggestion to include as a limitation, the failure to assess the psychological factors that may influence the QoL more than the physical factors. However, an assessment of the psychological factors was not considered as it did not form part of the objective of this study which focused on symptom assessment and clinical characteristics. Moreover,

psychological factors are not considered in the domain evaluated in PedsQL. Nevertheless, it is an important factor to consider that could potentially be analyzed in future studies.

### 3) The introduction :

1) The authors did not mention clearly the importance of the study at the end of the introduction , what this research will add to the literature, as the previous studies found clearly that the symptoms of pediatric cancer are associated with lower quality of life , which is nearly the same results of this study so what this study adds .

Response:

We are grateful for this suggestion, this was an incredibly important revelation as we had overlooked highlighting the first of its kind multiple screen tool SSPedi-BR and the positive affect it can have on the QoL of Brazilian pediatric patients. Prior to the validated scale in Brazilian portuguese, a multiple screen tool for prevalent symptoms had not been available to this population. Through the use of this screening tool, it will now be possible to assess prevalent symptoms among Brazilian pediatric patients, leading to early intervention of the symptoms thereby having a positive effect on QoL.

2) The authors did not mention studies that are held in the locality of the study which are important to be mentioned

The location of the study site has been added to the Introduction section. We thank Mr. Sehlo for bringing to our attention. The following sentence has now been added:

Response: "In this context, the aim of this study was to evaluate an association of prevalent symptoms and clinical characteristics on the QoL of pediatric cancer patients treated at a reference hospital in Brazil."

### 4) The results :

1) The sentence with an association with time since diagnosis for the proxy-reported version ( page 9, lines 6,7) should be deleted.

Response : We agree with Mr. Sehlo's suggestion. The sentence has been removed.

2) Under Relationship between the PedsQL and SSPedi-BR symptoms

The sentence , ( page 10 , lines 1-3) The symptoms "Feeling tired", "Throwing up or feeling like you may throw up" and "Constipation" were statistically related to the four domains: emotional, school functioning, physical and social (table 4) . While in reviewing table 4, all the symptoms that are screened by SSPedi-BR symptoms affect negatively PedsQL except changes in taste and diarrhea ( why all these affecting symptoms are not included in the paragraph)

Mr. Sehlo has made valid question in regards to the four symptoms highlighted in the aforementioned paragraph. In order to clarify any misunderstanding the paragraph has been rewritten in order to give a better understanding of the relationship between the symptoms and domains of two scales. The paragraph now reads:

Response:

"In the self-reported version the following symptoms: "Feeling disappointed or sad", "Feeling scared or worried" (reflective) ,and "Feeling cranky or angry" (Don't feel like smiling), presented a negative impact on QoL in the emotional domain. The symptoms of Mouth sores, and Constipation (hard to poop) presented a negative impact in the school domain. The symptoms of Hurt or pain (other than headache), and Throwing up or feeling like you may throw up, had an impact on the emotional and physical domain. A compelling finding was the identification of the symptom "Feeling tired" which had an impact on QoL of all four of the domains ( Emotional, School, Physical, Social).

The only symptom in the proxy-reported version that demonstrated an impact on QoL was the "feeling scared or worried" which had an impact on the emotional domain."

Also the sentence Regarding the proxy-reported version, only the emotional domain showed a relationship with symptoms on the SSPedi-BR scale: "Feeling scared or worried (concerned)" ( $p=0.001$ ), "Feeling more or less hungry (don't feel like eating) than you usually do" ( $p=0.048$ ) and "Changes in taste (flavor of food)" ( $p=0.031$ ). (page 10 , lines 4-7) , where is the table that reflecting these results

Response: We appreciate Mr. Sehol's request for the inclusion of the aforementioned data. A new table was constructed after a new analysis was completed demonstrating different results. ( Table 5)

#### 5) Discussion :

The discussion needs to be more deep to highlight the importance of the results

Response: In agreement with Mr. Sehol in regards to highlighting the results of the study in the discussion section, this section has been reviewed and rewritten.

Reviewer:2

Reviewer Name: Carsten Müller

Institution and Country: University Sports, University of Münster, Germany

Please state any competing interests or state 'None declared': None declared.

The manuscript entitled „Influence of multiple symptoms on the quality of life of pediatric cancer patients: a cross sectional study" represents a cross-sectional study examining the impact of numbers and severity of symptoms, assessed using the Symptoms Screening in Pediatrics Tool, on quality of life, assessed using the Pediatric Quality of Life Inventory (PedsQL) in pediatric oncology. Generally, the paper would benefit from reviewing of a native speaker/ language editing services. Although the study design and outcome variables seem appropriate, the manuscript would also benefit from a clarification of the objectives / primary outcome measures and statistical analyses. We would like to thank Mr. Müller for his thorough review and helpful suggestions. A complete overview of the paper was conducted and some of the sections were rewritten in order to provide greater clarification and understanding.

#### MAJOR:

The title "Influence of multiple symptoms on quality of life..." suggests a cause-effect-relationship that cannot be assessed in a cross-sectional study. I would propose to rephrase the title to "Association of symptoms, quality of life, and clinical characteristics in pediatric cancer patients – a cross sectional study"

The suggestion of the title change has been greatly appreciated. The new title now reads:

Response: "Association between multiple symptoms and Quality of Life of pediatric cancer patients in Brazil - a cross-sectional study."

Abstract, page 2, ll. 10-11: Bearing in mind that the objectives of the study were to evaluate the influence of multiple symptoms on quality of life (QoL), the primary outcome measure (dependent variable) is QoL (PedsQL), and the secondary outcome measures should be symptoms (SSPedi-Br). However, in this case, larger parts of the manuscript had to be rewritten, focusing on QoL in pediatric cancer patients and the dependency of QoL on the number of symptoms and symptom severity. As mentioned above and in order to do justice to the actual objective of the paper, I would suggest to focus on the associations of the outcomes (QoL and symptoms) and their association with clinical characteristics.

We would like to thank Mr. Müller for this suggestion. After a review of our paper and the suggestions provided by the reviewers, we found that it was necessary to reassess the objectives of the study.

Response : The objectives have been modified to "To identify and evaluate the influence of multiple symptoms along with clinical characteristics on the Quality of Life (QoL) of pediatric cancer patients in Brazil."



Statistical analysis: What is the reason for using Mann-Whitney tests to compare the various clinical characteristics and PedsQL scores, instead of using MANOVA models? E.g., in case that data lacked normal distribution, median and IQR should be presented (tables 3 and 4). Moreover, information on p-value adjustments due to alpha error accumulation following multiple testing are missing. This most likely will have implications on the interpretation and discussion of the results. Please also consider calculating effect sizes.

Response : As suggested by Mr.Müller, a new test on the data was conducted using the suggested MANOVA test and calculated the effect size. In addition the model was adjusted taking into consideration Pillais Trace and Post-Hoc test by Bonferroni. Effect size was added to the table. ( table 3, 4 and 5)

MODERATE:

Please provide information on the psychometric properties of the questionnaires used.

We thank Mr.Müller for this observation. The inclusion of the psychometric properties had been overlooked for the questionnaire PedsQL. This has now been added.

MINOR:

Abstract, page 2, ll. 8-9: exclusion criteria: please indicate how many patients and proxies had neuropsychiatric disorders and/or visual impairment (N=)

In response to Mr. Müller's request in regards to the suggestion above, the sentence that was located in the abstract that led to the confusion has been removed from the article. It gave the impression that some of the participants were excluded due to neuropsychiatric disorders. The intent was to indicate that neuropsychiatric disorders presented at the time of participation, were in fact a criteria for non-eligibility to participate in the study. This confusion has also been clarified in the Methods section.

Abstract, page 2, ll. 13-15: "... between the time of diagnosis and surgical procedure [on symptom severity]." For clarification purposes, please the text in brackets [...].

Based on the suggestion to clarify the objectives of this study, information on symptom severity and its effect on QoL has been removed. The objective of the study now focuses on the effects of multiple symptoms and clinical characteristics on QoL. We thank Mr. Müller for this suggestion.

Table 1: The authors refer to the educational level of the patients – however, no information on assessment of the educational level have been provided in the methods' section. Please clarify.

Response: This information had been collected, however after further analysis the information regarding a patient's education level was excluded from the study.

Please make consistent use of the PedsQL throughout the manuscript, because there are at least four different spellings.

Response: We would like to thank Mr. Müller for catching this oversight. We have gone through and reviewed the use of (PedsQLTM) within the article to ensure consistency in spelling.

Page 4, l. 9: Please consider rephrasing "objective" in connection with self-reports. Maybe "valid" and/or "reliable" fits better?

We would like to thank Mr. Müller for making this suggestion. We have made the edit to the paper.

Conclusion: page 12, ll. 15-17: it says "The present study shows that pediatric patients experienced a higher prevalence of symptoms during treatment ..." It is unclear to whom the authors refer. A higher prevalence of symptoms compared to...?

Confusion was in relation to the use of the comparative word "higher". The statement was rewritten to indicate a "high" number of symptoms. The sentence now reads:

“The present study shows that pediatric patients experienced a higher prevalence of symptoms during treatment and that quality of life in the emotional domain was negatively and significantly influenced. In addition, an assessment of clinical characteristics did not demonstrate any significant effect on QoL. These results demonstrate the importance of the use of instruments such as the SSPedi-BR in the management and control of symptoms during clinical practice.

“and that quality of life in the social emotional domain was negatively and significantly influenced” Again, during treatment refers to “time of diagnostic”? or “inpatient vs. outpatient clinic”? Please clarify.

Response: Sentence was reviewed and rewritten in order to clarify the misunderstanding.

We would like to thank the reviewers for this important contribution.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Prof Mohammad Gamal Sehlo Professor of Psychiatry - Zagazig University - Zagazig - Egypt
<b>REVIEW RETURNED</b>	03-Feb-2020

<b>GENERAL COMMENTS</b>	<p>the paper is now in this first revision well written and well organised and many of it's previous mistakes is now corrected. Just needs a brief addition , please in the results under the abstract in (page 3 , lines from 3-7) add the exact results of the study in brief beside the the effect of feeling tired. also in the conclusion under the abstract (page 3 line 14) please rewrite this line as follows Pediatric cancer patients with severe symptoms during treatment resulted in a negative impact on all aspects of quality of life especially the emotional domain of QoL.</p> <p>Also in the final conclusion (page 15 - line 35) rewrite this line to be a higher prevalence of symptoms during treatment and that quality of life in all aspects especially the emotional domain were negatively and significantly influenced.</p>
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<b>REVIEWER</b>	Carsten Müller University of Münster, University Sports
<b>REVIEW RETURNED</b>	21-Jan-2020

<b>GENERAL COMMENTS</b>	<p>Thank you to the authors for performing a comprehensive revision of the manuscript. Although the manuscript has gained clarity, there are still several (minor) points that should be addressed in a minor revision.</p> <p>Firstly, though improved, the manuscript would still benefit from language editing service or revision of a native speaker.</p> <p>Secondly, the authors have changed the title from “Influence of” to “Association between...” thus acknowledging the fact that a cross-sectional study has clear limitations when addressing cause-effect relationships between variables. However, already in their first line of the abstract it says “...evaluate the influence of multiple symptoms [...] on the Quality of Life (QoL) of pediatric cancer patients”. This kind of wording specifies a direction of the relationship between the variables that cannot be addressed using a cross-sectional analysis. How can the authors be confident that</p>
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	<p>there is no bidirectional relationship between the variables examined, for instance. I suggest – once again – to carefully revise the whole manuscript regarding this kind of wording and use the term “is associated with” instead of “has an impact on...”.</p> <p>Section “Strengths &amp; limitations”  4th bullet point: rephrase to “We report the results of a single-center study”  5th bullet point: Here, the authors need to clarify their statement. In the methods’ section it says: “patients [...] undergoing chemotherapy at any stage of treatment”. As patients were evaluated at any stage of treatment, the study indeed evaluated different stages of treatment. I guess, the authors refer to the fact that each patient was evaluated once (which is identical to the penultimate bullet point).</p> <p>Page 6, line 25: the authors describe the SSPedi-BR. Information is missing that it assesses symptoms on a 5-point-Likert scale (0-4).  Page 6, line 32: Refer to reference 18 at this point and provide information about validity and reliability (e.g. ICC coefficients) here.  Page 6, line 55 &amp; page 7 line 3: this is a repetition of the penultimate sentence  Page 7, lines 12/13: “PedsQLTM) generic questionnaire proved to be valid and reliable” Please be more specific in terms of validity and reliability coefficients.  Page 7, line 21/22: why is “the city of origin” of interest? Can be deleted</p> <p>Page 9, lines 38-43: “[Symptoms] were more frequent [...]”. More frequent to whom? Firstly, there are three age groups. It should be clarified to which group/comparison the p-values refer to. Secondly, the decision for building these three age groups seems rather arbitrarily and is not clear to the reader. Why not use a regression analysis with age as predictor when the authors want to show that older adolescents more frequently report specific symptoms compared to children?</p> <p>Table 2: Odds ratios are presented. The calculation of ORs should also be mentioned in the methods’ section - statistical analysis.</p> <p>Table 3: The same applies to the effects sizes presented in table 3: calculation of effect sizes should be mentioned in the methods’ section - statistical analysis. Please also give information on how effect sizes were calculated.</p> <p>Page 7, line 41: I already noted it in the first review, and the authors have answered clarifying to this point, but forgot to change it in the manuscript: “pediatric patients experienced a high[er] prevalence of symptoms”</p>
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## VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Carsten Müller

Firstly, though improved, the manuscript would still benefit from language editing service or revision of a native speaker.

We can understand Mr. Müller's suggestion. It is difficult to ensure that all the information, ideas, and essence of a paper are properly translated into English. At times, due to limitations in vocabulary and differences in grammar sentence structure, ideas that are clearly transmitted and presented in Portuguese, fall short when translated. This current document had previously gone through a reputable translation service and a secondary review was completed by a native speaker. Taken Mr. Müller's suggestion, we have once again requested the service of a native speaker to review our paper.

Secondly, the authors have changed the title from "Influence of" to "Association between..." thus acknowledging the fact that a cross-sectional study has clear limitations when addressing cause-effect relationships between variables. However, already in their first line of the abstract it says "...evaluate the influence of multiple symptoms [...] on the Quality of Life (QoL) of pediatric cancer patients". This kind of wording specifies a direction of the relationship between the variables that cannot be addressed using a cross-sectional analysis. How can the authors be confident that there is no bidirectional relationship between the variables examined, for instance. I suggest – once again – to carefully revise the whole manuscript regarding this kind of wording and use the term "is associated with" instead of "has an impact on...".

We greatly appreciate the author's comments in this regard. We have conducted a review of our manuscript as suggested and made the necessary edits in the text.

#### Section "Strengths & limitations"

4th bullet point: rephrase to "We report the results of a single-center study"

We appreciate the suggestion to use a phrase that is more commonly used.

5th bullet point: Here, the authors need to clarify their statement. In the methods' section it says: "patients [...] undergoing chemotherapy at any stage of treatment". As patients were evaluated at any stage of treatment, the study indeed evaluated different stages of treatment. I guess, the authors refer to the fact that each patient was evaluated once (which is identical to the penultimate bullet point).

We thank Mr. Müller for highlighting this oversight. The original text was indeed a little confusing. The sentence has been rewritten to give the understanding that all patients must be undergoing chemotherapy. In addition, undergoing chemotherapy has been included in the criterion for the inclusion of this study. The sentence now reads as follows: Analysis of each patient was completed regardless of the stage of treatment.

Page 6, line 25: the authors describe the SSPedi-BR. Information is missing that it assesses symptoms on a 5-point-Likert scale (0-4).

This information in regards to the Likert scale had been in the original document and during the last edit was accidentally removed. We have reinserted this information. We thank Mr. Müller for bringing to our attention.

Page 6, line 32: Refer to reference 18 at this point and provide information about validity and reliability (e.g. ICC coefficients) here.

We thank Mr. Müller for this insight. We have added the requested information regarding validity and reliability.

Reliability :The internal consistency was verified using Cronbach's alpha test, with values of  $\alpha=0.77$  (95% CI 0.70 to 0.82) for the self-reported version,  $\alpha=0.81$  (95% CI 0.71 to 0.88) for the proxy-reported version.

Reproducibility test-retest :The ICC (95% CI) values were 0.77 (0.64 to 0.86) for the self-reported version, 0.54 (0.15 to 0.77) for the proxy-reported version.

The construct validity was tested according to the convergent validity and contrasted groups validity. The correlation values of the coefficients were considered good ( $r \geq 0.4$ ).<sup>35</sup>

Page 6, line 55 & page 7 line 3: this is a repetition of the penultimate sentence

We have reviewed the aforementioned sentence. The following edit has been made.

Page 7, lines 12/13: "PedsQLTM) generic questionnaire proved to be valid and reliable" Please be more specific in terms of validity and reliability coefficients.

We have added the validity and reliability coefficients for PedsQLTM. We thank Mr. Müller for bringing to our attention. The reliability was evaluated using the Cronbach alpha test. The test values were between 0.6 and 0.9 for all the dimensions demonstrating adequate internal consistency. The construct validity for the Brazilian version of PedsQLTM 4.0 demonstrated high levels of correlation between the domains. Physical domain ( $r = 0.77$ ,  $p < 0.001$ ), school ( $r = 0.73$ ,  $p < 0.001$ ), emotional and social ( $r = 0.40$  e  $0.59$ , respectively,  $p < 0.001$ ).

Page 7, line 21/22: why is "the city of origin" of interest? Can be deleted

We have reviewed the statement "the city of origin" and have found it unnecessary in the text. It has been removed. We are grateful for this suggestion.

Page 9, lines 38-43: "[Symptoms] were more frequent [...]". More frequent to whom? Firstly, there are three age groups. It should be clarified to which group/comparison the p-values refer to. Secondly, the decision for building these three age groups seems rather arbitrarily and is not clear to the reader. Why not use a regression analysis with age as predictor when the authors want to show that older adolescents more frequently report specific symptoms compared to children?

We are thankful for Mr. Müller's comments regarding age and frequency of symptoms. There was a misunderstanding due to the original wording of the paragraph. The paragraph has been rewritten in order to clarify the confusion. The p-values refers to all of the age groups. The decision to classify the participants into three different age groups was based on the pattern set by the researchers in a previous study that had described the symptoms of pediatric patients while using the SSPedi screening tool. Maintaining this pattern allowed us to see an increase in the frequency of the symptoms related to the 15 to 18 years of age group.

A regression analysis was completed in regards to the severity of symptoms between the age groups. A significant difference in the severity of the symptoms reported was not found therefore, the results were not reported in this study. Furthermore the study aimed to analyze the relationship of symptoms on quality of life and not based on the different age groups.

Table 2: Odds ratios are presented. The calculation of ORs should also be mentioned in the methods' section - statistical analysis.

We would like to thank Mr. Müller's suggestion and have mentioned the ORs in the methods section.

Table 3: The same applies to the effects sizes presented in table 3: calculation of effect sizes should be mentioned in the methods' section - statistical analysis. Please also give information on how effect sizes were calculated.

We thank Mr. Müller for this suggestion and have added the information regarding the calculation of the effect size in the methods section under statistical analysis.

Page 7, line 41: I already noted it in the first review, and the authors have answered clarifying to this point, but forgot to change it in the manuscript: "pediatric patients experienced a high[er] prevalence of symptoms"

After reviewing the sentence we feel that we have been able to modify the wording in order to better describe our findings without causing confusion between severity and number of prevalent symptoms. The sentence now reads as follows:

The present study shows that the prevalence of symptoms experienced among pediatric patients during treatment was high and that quality of life in all aspects especially in the emotional domain was negatively and significantly influenced.

Reviewer: 1

Reviewer Name: Prof Mohammad Gamal Sehlo

Institution and Country: Professor of Psychiatry - Zagazig University - Zagazig - Egypt

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

the paper is now in this first revision well written and well organized and many of its previous mistakes is now corrected. Just needs a brief addition , please in the results under the abstract in (page 3 , lines from 3-7) add the exact results of the study in brief beside the the effect of feeling tired. We would like to thank Mr. Mohammad for this suggestion. After further analysing our results and to ensure clarity of the abstract, we opted to simplify the sentence to address the findings regarding the association of clinical characteristics and symptoms on QoL. A detailed description of the results has already been described in the paper.

also in the conclusion under the abstract (page 3 line 14) please rewrite this line as follows Pediatric cancer patients with severe symptoms during treatment resulted in a negative impact on all aspects of quality of life especially the emotional domain of QoL.

Once again we would like to thank Mr. Mohammad for this suggestion. We have added the sentence recommended and agree that it aids in clarifying the point.

Also in the final conclusion (page 15 - line 35) rewrite this line to be a higher prevalence of symptoms during treatment and that quality of life in all aspects especially the emotional domain were negatively and significantly influenced.

We are grateful for Mr. Mohammad's suggestion to rewrite the sentence in our conclusion. Though we did not use the same wording, we feel we were able to capture the essence of what Mr Mohammad had suggested to be highlighted in regards to all aspects of QoL.

We would like to thank the reviewers for this important contribution.

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Carsten Müller University of Münster, Germany
<b>REVIEW RETURNED</b>	10-Mar-2020
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