

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Measuring the impact of COVID-19 on the quality of life of the survivors, partners and family members: A cross-sectional international online survey
AUTHORS	Shah, Rubina; Ali, Faraz; Nixon, Stuart; Ingram, John; Salek, Sam; Finlay, Andrew

VERSION 1 – REVIEW

REVIEWER	Claudia Bargon UMC Utrecht
REVIEW RETURNED	05-Jan-2021

GENERAL COMMENTS	<p>The current analysis adds to the emerging literature regarding how COVID-19 affects (ex)COVID-19 patients and their families. It is a clear report of PRO outcomes during the pandemic in a global consortium, using the modern methods of social media. It is well written, and overall the subject is of importance in this COVID-19 era.</p> <p>Many of the results are perhaps as expected, but statistical confirmation of those results is a strength. Some other strengths are the use of the validated questionnaire EQ-5D-3L, and it's nice to see the use of FROM-16 in the context of COVID-19. The authors were able to reach a great sample size of > 700 COVID-19 survivors and a similar amount of family members/ partners.</p> <p>I agree with the authors that PROs are very relevant these days, and as little is known about PROs during COVID-19, I congratulate the authors on this initiative. Some major and minor comments are listed below:</p> <ol style="list-style-type: none"> 1. It is hard to draw conclusions from this cross-sectional study without any knowledge of baseline measurements (preferably pre-COVID-19). A major limitation of this study is that you can't differentiate between the effect of COVID-19 infection, or perhaps a pre-existing physical or mental state. Please discuss this limitation. 2. The study was conducted between June and August 2020. I can imagine that the severity of the pandemic varied among the different countries/ continents at that time, and many PROs might have been influenced by the specific local, governmental measures that were taken at the time. Please describe or discuss this limitation, and can we account for it? 3. Now that the pandemic is still lingering, it would be interesting to see follow-up data. Could the authors discuss recommendations or plans for further follow-up studies?
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	<p>4. The authors recruited their participants through social media. Although this is a very efficient and easy way to quickly recruit many participants for a study with such a timely subject, I have some major concerns that should be addressed.</p> <p>First, the validated questionnaires were only available in English, so to my knowledge, the questionnaires are only truly validated on native English speaking participants. As participants were recruited globally, I have concerns about the validity of the scores of those who do not speak English that well. Did you consider this validity issue?</p> <p>Second, how were the patients diagnosed with the COVID-19 infection? Or how did the authors make sure all participants were truly tested and COVID-19 positive? I think it is patient-reported, however, how can we ensure that participants really were tested positive for COVID-19?</p> <p>Third, especially in outcomes like PROs, cultural differences might play a crucial role in the outcome. Did the authors account for this?</p> <p>Fourth, as the authors already mention; a major limitation of their inclusion method is selection bias. This indeed leads to generalization problems. The authors should take this into account in their conclusions.</p> <p>5. The authors included some clinically relevant variables, however, some are not very specific. Is there any information on the definition of "hospitalization"? I strongly believe that there is a great difference of the effect of hospitalization with or without admission the ICU. Also, please specify "existing health condition" or define this.</p> <p>6. It is interesting to read the effect of the duration of symptoms on PROs. Additionally, relevant to the PROs could also be how time had passed since their recovery, and how do you define "recovery"? Please clarify.</p> <p>7. Especially when using PROs, the clinical significance of a paper is not only explained by statistical significance. Please discuss threshold scores for clinical importance for the outcomes.</p> <p>8. Please discuss the limitation that there is no healthy reference group (i.e., age- and / or living area- matched) to compare the EQ-5D outcomes of the COVID-19 survivors to.</p> <p>9. The authors did a great effort to collect a great amount of data. However, in my opinion there are too many tables and figures, and therefore the paper lacks focus. Please try to focus on the most important findings in both the results and tables/figures. It might be sufficient to only mention the less relevant findings in the text.</p> <p>10. Although not incorrect, in the "statistical methods" section the methods for descriptive statistics are very briefly mentioned and deserve more attention.</p> <p>11. I would be interested in the authors thoughts on why the great majority of survivors were female.</p> <p>12. Although the authors list great solutions for clinical implications, more detailed research should be performed in order to identify the</p>
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	<p>true needs of COVID-19 survivors and their family. Please address this nuance in your discussion.</p> <p>13. Please specify the definition "long COVID"; what timeframe is meant by 'persisting'?</p> <p>14. Line 38 "Outcome : The primary outcome was to measure the impact of COVID-19 on survivors and their partners and family members. Exposure: Person's COVID-19 infection and its impact on partners and family members.". Please change outcome to "the impact of COVID-19 on the quality of life of survivors and their partners and family members. Exposure: COVID-19 infection of participant or of the family member".</p>
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REVIEWER	Himali Weerahandi NYU Langone Health
REVIEW RETURNED	22-Jan-2021

GENERAL COMMENTS	<p>Overall Comments: Thank you for the opportunity to review this manuscript. This is an interesting, large, international cross-sectional study examining the impact of COVID-19 on QoL of survivors and their family members. I don't think many studies have examined the impact COVID-19 has had on family members, so this is an important contribution. In addition, the researchers sought feedback from a patient and family members during survey development, which is to be commended. I do have some questions for clarification regarding the survey methods and statistical analyses, which are detailed below.</p> <p>Major comments</p> <p>Methods:</p> <ul style="list-style-type: none"> - Is EQ-5D the same thing as EQ-5D 3 level? These terms seem to be used interchangeably throughout the manuscript, but it's not clear that they are referring to the same thing. - page 4, lines 56-59: "The study was only open to individuals who were diagnosed with COVID-19 and their family member or partner" <ul style="list-style-type: none"> o How was COVID-19 diagnosis confirmed? If this was self-report only (without objective verification), this should be made clear. - page 7, lines 48-53: "Section two was completed by the partner or a close family member of the survivor who provided basic demographic details and completed FROM-16." <ul style="list-style-type: none"> o How did the investigators or the participant decide that a partner or close family member should fill out the survey? Did the family member have to be someone the patient lives with, or could be any close relation? - page 8, line 34 specifies that the FROM-16 is available in several languages which contradicts the reasoning in the limitations section, "the study materials were available only in the English language" - page 8, lines 38-40: "The primary outcome was to measure the impact of COVID-19 on survivors and their partners and family members." <ul style="list-style-type: none"> o Please provide more details about the analyses. Was the dependent variable the total EQ-5D 3 level scores/ FROM-16 scores? Was the EQ-VAS score added to the EQ-5D 3 level score? Looking at Table 5, it seems that EQ-VAS is scored separately.
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	<p>o While the Statistical analysis states, “Spearman’s rank correlation coefficient and multiple regression analysis were conducted to understand the effect of independent variables (i.e. predictors) on the EQ-5D and FROM-16 outcomes,” the investigators need to specify exactly what predictors were in these models (were they all the variables listed in Table 1? Or just the variables listed in Table 6? Did you decide what went into the model based on which correlations were significant? If so, this should be specified).</p> <p>o The investigators state “To determine differences between groups defined by each outcome chi-square tests (when appropriate, Fisher’s exact tests) and Mann-Whitney U tests were computed.</p> <p>□ Please provide more detail on what these group comparisons were. Were these bivariate comparisons based on patient/family member characteristics? In Table 3 it looks like you reported bivariate outcomes on 3 patient characteristics (gender, pre-existing health condition, and hospitalization). This is fine, but should be detailed in the methods section. Also a rationale as to why you chose to examine these characteristics over others that could also potentially have an effect on the score (such as age, occupation, etc). I do see that Table 5 reports correlations but it is unclear to me what this table is reporting. Is it the spearman correlation coefficient between EQ-5D and the other variables? If so, shouldn’t the spearman correlation coefficient be 1 for EQ-5D to itself?</p> <p>- page 8, lines 38-40: “Covariates: The covariates included hospital stay due to COVID-19 infection, existing health condition of survivors, duration of COVID-19 infection”</p> <p>o If data about hospitalization, existing conditions, duration of infection were reported by the patient, please make this clear. Self-reported data on hospitalization and medical problems could be inaccurate and is a potential limitation. (see: Caraballo C, Khara R, Jones PG, et al. Rates and Predictors of Patient Underreporting of Hospitalizations During Follow-Up After Acute Myocardial Infarction: An Assessment From the TRIUMPH Study. <i>Circ Cardiovasc Qual Outcomes</i> 2020;13:e006231)</p> <p>Results</p> <p>- Similar to the Body Politic COVID-19 study (Hannah E. Davis, Gina S. Assaf, Lisa McCorkell, Hannah Wei, Ryan J. Low, Yochai Re’em, Signe Redfield, Jared P. Austin, Athena Akrami, Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact,” medRxiv 2020.12.24.20248802), the respondents are mostly women—it’s worth noting with respect to generalizability of the findings because men are more likely to be admitted to the hospital for COVID-19. I also wish race data was collected, particularly given the disproportionate effect COVID-19 has had on immigrant and BIPOC communities.</p> <p>- page 12, line 26-31, “There was a significant gender difference for ‘mobility’ and for ‘pain and discomfort’ ($p \leq 0.05$) with females being more impacted than males (Fig 1).”</p> <p>o However, Figure 1 does not report gender differences. Do you mean Table 3?</p> <p>- page 16, lines 24-27: “There was a significant positive association between the family members’ FROM-16 scores and the survivors’ EQ-5D scores ($p < 0.001$) (Fig 4)”</p> <p>o I think you are referring to the figure that is labeled as figure 3. Could you provide details on how you established that this is a positive correlation between these scores? Is it based on the</p>
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	<p>spearman’s correlation coefficient reported in Table 5? The data you have displayed in the Figure does not look convincing that there is a positive relationship (despite the diagonal line drawn---how was this line calculated?), and in fact looks fairly spread out evenly.</p> <p>- page 16, lines 33-41: “However, other variables such as hospital stay, existing health condition, number of weeks since COVID-19, survivors’ age and gender indicated that being female or being older was associated with lower EQVAS scores ($p < 0.05$), that is lower health status.”</p> <p>o I’m confused as I thought you were reporting correlations between EQ-5D and the other characteristics, and not between EQVAS and the patient/family member characteristics.</p> <p>Tables</p> <p>- Table 5: please explain what the 1-10 in the top column means.</p> <p>- Tables 6 and 7: Please specify which gender was the reference for the multivariable analyses.</p> <p>Discussion</p> <p>- page 20, lines 35-41: “Survivors with existing health conditions did not differ significantly from those without such conditions except for mobility. and having an existing health condition was not a significant predictor of impact on the family member/partner’s QoL.”</p> <p>o I would temper this statement as existing health conditions were self-reported and also all medical problems were lumped together--- patients with just hyperlipidemia are likely to be different from a patient with more serious medical conditions (such as heart failure).</p> <p>- Additional limitations for study include that it does not follow a pre-specified cohort, rather patients opt in to report their symptoms. People who are experiencing symptoms may be more likely to participate in a study such as this versus those who have gotten completely better and moved on with their lives.</p> <p>Minor comments</p> <p>Introduction</p> <p>- page 3-4 lines 57-60: This sentence about the FROM-16 and explaining its suitability for this study would fit better in the Methods section rather than the Introduction section.</p> <p>Tables</p> <p>- Table 1: would report interquartile range to correspond with median fore age and duration of COVID-19 symptoms. You report the full range, which is interesting, but the IQR usually is also reported.</p> <p>- Table 1: occupation, for the group that is in paid work, would be interesting to know if these participants work from home (I know that’s not possible at this time to collect that data, but just food for thought).</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
(Dr. Claudia Bargon, UMC Utrecht)

Comments to the Author:

The current analysis adds to the emerging literature regarding how COVID-19 affects (ex)COVID-19 patients and their families. It is a clear report of PRO outcomes during the pandemic in a global

consortium, using the modern methods of social media. It is well written, and overall, the subject is of importance in this COVID-19 era.

Many of the results are perhaps as expected, but statistical confirmation of those results is a strength. Some other strengths are the use of the validated questionnaire EQ-5D-3L, and it's nice to see the use of FROM-16 in the context of COVID-19. The authors were able to reach a great sample size of > 700 COVID-19 survivors and a similar amount of family members/ partners.

I agree with the authors that PROs are very relevant these days, and as little is known about PROs during COVID-19, I congratulate the authors on this initiative.

Response:

Thank you for your appreciation.

Some major and minor Comments are listed below:

Comment 1:

It is hard to draw conclusions from this cross-sectional study without any knowledge of baseline measurements (preferably pre-COVID-19). A major limitation of this study is that you can't differentiate between the effect of COVID-19 infection, or perhaps a pre-existing physical or mental state. Please discuss this limitation.

Response:

Thank you for raising this very important point. We have now elaborated this point further in the Limitations section of the Discussion, which now reads as below:

“Because of the nature of the study, we could not collect any baseline measurements (pre-COVID-19 measurements). We are, therefore, not able to differentiate between the effect of COVID-19 infection or of a pre-existing physical or mental state. However, only 30.9% of respondents had any existing health condition, and therefore this limitation only refers to this small proportion of respondents”.

Comment 2:

The study was conducted between June and August 2020. I can imagine that the severity of the pandemic varied among the different countries / continents at that time, and many PROs might have been influenced by the specific local, governmental measures that were taken at the time. Please describe or discuss this limitation, and can we account for it?

Response:

Thank you for drawing our attention to this limitation of our study. We have added the following to the Limitations section of the Discussion:

“Furthermore, the study was carried out between June and August 2020 when the severity of the pandemic varied among different countries. Therefore, the study results may have been influenced by the specific local and governmental measures in place at the time. It is likely that participants will have been living under different government restrictions, thereby possibly influencing responses to the questionnaires. However, because of the complexity of the international situation, we are not able to account for this”.

Comment 3:

Now that the pandemic is still lingering, it would be interesting to see follow-up data. Could the authors discuss recommendations or plans for further follow-up studies?

Response:

Thank you for your comment. We have changed the title of this section of the Discussion from 'unanswered questions and future research' to "**Future research and recommendations**". We have also added the following to this section of the manuscript:

"As COVID-19 is still a major challenge, with people experiencing 'long COVID', there is a need for further research including long term studies to better understand 'long COVID' and its impacts on survivors and family members. However, the way the participants were recruited for the current study does not allow us to have access to follow-up data from this cohort".

Comment 4:

The authors recruited their participants through social media. Although this is a very efficient and easy way to quickly recruit many participants for a study with such a timely subject, I have some major concerns that should be addressed.

Response:

Thank you for raising these concerns. We have addressed them below:

Comment 4a:

First, the validated questionnaires were only available in English, so to my knowledge, the questionnaires are only truly validated on native English speaking participants. As participants were recruited globally, I have concerns about the validity of the scores of those who do not speak English that well. Did you consider this validity issue?

Response:

Thank you for this helpful and relevant comment. We have added the following to the Limitation section of the Discussion:

"This survey was conducted internationally in the English language. The ability of some respondents to read and understand English may have been limited, but we are not able to assess this. However, during the development of, in particular, FROM-16, the following issues were considered as part of its conceptualisation and development in order to improve its universality and translatability: 1) applying readability to the level of understanding of a 12 year old; 2) formatting of the items into short and complete sentences of about six words to enhance clarity of meaning; 3) ensuring ease of understanding to allow future cross-cultural adaptation, facilitating universality and translatability. Although we did not develop the EQ-5D, that questionnaire was also designed to be as universally understandable as possible.

Concerning the wider survey questions, we took several steps in the development of the survey to ensure maximum comprehensibility: 1) We ensured that the readability was acceptable to a 12-year-old standard; 2) We carried out an international pilot including participants for whom English was not their first language and made adjustments accordingly; 3) The survey was reviewed by our patient study research partners".

Comment 4b:

Second, how were the patients diagnosed with the COVID-19 infection? Or how did the authors make sure all participants were truly tested and COVID-19 positive? I think it is patient-reported, however, how can we ensure that participants really were tested positive for COVID-19?

Response:

Thank you for this inquiry. In our study, all COVID-19 infections were patient-reported, and the study is based on the lived experience of COVID-19. We are sorry that we cannot clarify whether all of the patient participants had tested positive, but all confirmed that they had been infected with COVID-19. We tried to keep the survey as simple as possible without using medical language to make it user friendly. However, family members also answered the survey about the impact of their relative's COVID-19 on themselves; this provided further authentication of the patient's COVID-19 infection. We have, therefore, added the following to the Discussion:

"The survey depended on the patient's self-report of the diagnosis of COVID-19 infection and did not specifically ask whether patients had had a COVID-19 positive test. However, further authentication of the diagnosis is given by both the patient and their relative having answered the survey."

Comment 4c:

Third, especially in outcomes like PROs, cultural differences might play a crucial role in the outcome. Did the authors account for this?

Response:

Thank you for raising this point. Yes, we agree that cultural difference can play an important role in the outcome. We have now added the following to the Limitation section of the Discussion section of the manuscript:

"Although formal cultural adaptation of the survey questionnaire was not carried out, we endeavoured to ensure maximum understandability and acceptability. It should be noted that the questions asked are mostly universal in nature and do not refer to culturally specific practices such as semantic differences".

Comment 4d:

Fourth, as the authors already mention; a major limitation of their inclusion method is selection bias. This indeed leads to generalisation problems. The authors should take this into account in their conclusions.

Response:

Thank you for this Comment. While we agree that the possibility of selection bias is a major limitation of the study, but the methodology used was the most efficient, and safest, way of reaching COVID-19 survivors during the pandemic. We have now added the following to the conclusion:

"Although the recruitment method used inevitably leads to some degree of selection bias which in turn may dilute the generalisability of the study findings, the central conclusions of this study, that COVID-19 has a profound and long-lasting impact on survivors and their family members continue to remain valid".

Comment 5:

The authors included some clinically relevant variables; however, some are not very specific. Is there any information on the definition of "hospitalisation"? I strongly believe that there is a great difference of the effect of hospitalisation with or without admission the ICU. Also, please specify "existing health condition" or define this.

Response:

Thank you, please find below our point-by-point response.

Comment 5a:

The authors included some clinically relevant variables, however, some are not very specific. Is there any information on the definition of "hospitalisation"? I strongly believe that there is a great difference of the effect of hospitalisation with or without admission the ICU.

Response:

Thank you for pointing this out. Concerning the question of possible difference between the effect of hospitalisation with or without admission to ICU, we agree that this is a way to differentiate between the seriousness of the disease, which may have an impact on the later quality of life. However, examining such a difference was not one of the aims of our study; therefore, our survey did not ask this question. In planning the survey, we decided to keep it as simple as possible to ensure high levels of participation. We have now added the following to the Discussion section of the manuscript:

"This survey did not ask respondents whether those hospitalised were admitted to ICU. So we are not able to draw any conclusion concerning the relationship of admission to ICU to later QoL".

Comment 5b:

Also, please specify "existing health condition" or define this.

Response:

Thank you for your comment. We have added the following to the Discussion section of the manuscript:

"In the survey, COVID-19 survivors were asked whether they were 'already suffering from some existing chronic health condition (such as diabetes, heart disease, lung disease)' prior to the infection with COVID-19".

We have also now replaced term 'pre-existing health condition' with "existing health condition" in the manuscript and in the tables to be consistent throughout.

Comment 6:

It is interesting to read the effect of the duration of symptoms on PROs. Additionally, relevant to the PROs could also be how time had passed since their recovery, and how do you define "recovery"? Please clarify.

Response:

Thank you for your Comment. In the survey, we did not specify recovery as we felt that this would be impossible to define and anyway, many of the respondents indicated by their responses that they had not fully recovered. The coining of the descriptor "long-COVID" reflects this reality. We asked "how many weeks was it since the patient first had COVID-19"; this question relates to a clearly defined time. To clarify this, we have changed the following descriptor in the manuscript and Tables 5-7 from:

'Duration of COVID-19' to "Weeks since first had COVID-19".

Comment 7:

Especially when using PROs, the clinical significance of a paper is not only explained by statistical significance. Please discuss threshold scores for clinical importance for the outcomes.

Response:

Thank you for raising this very important point. In fact, we have currently just received ethical permission to start a study to address the clinical significance of FROM-16 scores in both clinical practice and research. However, this information is not currently available. Therefore, we have now added the following to the Discussion section of the manuscript:

“Currently Minimal Clinically Important Difference (MCID) for FROM-16 has not been published; however, MCID values for such questionnaires usually are approximately 10-20% of the total score range, and so we would expect the FROM-16 MCID to be approximately 3 to 6. If this is the case, the statistically significant differences reported would also be clinically significant”.

Comment 8

Please discuss the limitation that there is no healthy reference group (i.e., age- and / or living area-matched) to compare the EQ-5D outcomes of the COVID-19 survivors to.

Response:

Thank you for raising this. Our study was not designed to measure EQ-5D values in a healthy reference group. However, there are considerable data from the use of EQ-5D in different countries within Europe and worldwide. While not strictly comparable, we have now quoted some healthy reference group EQ-5D data for the UK to give the reader a sense of the meaning of EQ-5D scores. We have therefore added the following in the Limitation section of the Discussion:

“This study does not have a control group but in healthy volunteers in the UK, mean EQ-5D scores were EQ-VAS = 82.75, Mobility = 0.18, Self-Care = 0.04, Usual Activity = 0.16, Pain/Discomfort = 0.33, Anxiety / Depression = 0.20 (Szende and Janssen, 2014). In contrast, COVID-19 survivors (47.1% of the survey respondents were from the UK) in our study had mean scores of EQ-VAS = 55.83, Mobility = 1.59, Self-Care = 1.23, Usual Activity = 2.06, Pain / Discomfort = 1.93, Anxiety / Depression = 1.84. This suggests that overall HRQoL was highly impaired in the COVID-19 survivors across all domains.

We have added the following reference to the reference list section of the manuscript:

Szende, A. & Janssen, B. 2014. Cross-Country Analysis of EQ-5D Data. *In*: Szende, a., Janssen, B. & Cabases, J. (eds.) *Self-Reported Population Health: An International Perspective based on EQ-5D*. Dordrecht: Springer Netherlands.

Comment 9:

The authors did a great effort to collect a great amount of data. However, in my opinion there are too many tables and figures, and therefore the paper lacks focus. Please try to focus on the most important findings in both the results and tables/figures. It might be sufficient to only mention the less relevant findings in the text.

Response:

Thank you for this very helpful comment. We agree that the focus of the manuscript could be sharpened by reducing the number of figures. We have now deleted Figures 3 and 4 as information given in these figures is already mentioned in the manuscript. In addition, the changes we have introduced in the manuscript now focus on the most important findings of the study.

Comment 10:

Although not incorrect, in the “statistical methods” section the methods for descriptive statistics are very briefly mentioned and deserve more attention.

Response:

Thank you for this Comment. We have now added more information on descriptive statistics to the Methods section of the manuscript, which reads as follows:

“Descriptive statistics (i.e. mean, standard deviation, median, inter-quartile range) were performed for all variables”.

Comment 11:

I would be interested in the authors thoughts on why the great majority of survivors were female.

Response:

Thank you for this Comment. This is something that surprised us as well, especially as it is reported that men are more severely impacted by COVID-19 than women. However, the majority of social media COVID-19 support groups were started by women who had COVID-19 and hence attracted more female attention. Women in general tend to have a more caring attitude and are ready to share their experiences to help and support others. This could be the reason why women responded more. Another reason could be that women may have suffered post-COVID symptoms more than men and hence were more interested in the survey to raise awareness about it. We have therefore added the following text to the Discussion section of the manuscript:

“Interestingly of the patients who participated, most (76.6%) were women, as found in other surveys (Davis et al. 2020); however, there was a higher proportion of men among participating family members (66.5%). This may be because the majority of COVID-19 social media support groups have been initiated by women (patients), and the most convenient family person to ask to participate might be their partners (mostly male)”.

Comment12:

Although the authors list great solutions for clinical implications, more detailed research should be performed in order to identify the true needs of COVID-19 survivors and their family. Please address this nuance in your Discussion.

Response:

Thank you for pointing this out. We have already added this information to the ‘Future research and recommendations’ section of the manuscript in response to your Comment 3 as follows:

“As COVID-19 is still a major challenge with people experiencing ‘long COVID’, there is a need for further research including long term studies to better understand ‘long-COVID’ and its impacts on survivors and family members. However, the way the participants were recruited for the current study does not allow us to have access to data from follow-up of this cohort”.

Comment 13:

Please specify the definition “long COVID”; what timeframe is meant by ‘persisting’?

Response:

Thank you for this useful suggestion. We have now added the NICE 2020 definition of ‘long COVID’ and also defined what we mean by the term ‘persisting’ in the Discussion section of the manuscript, which reads as follows:

“According to NICE, the term ‘long COVID’ is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more)” (NICE, 2020).

“The term ‘Persisting’ refers to the continuity of the impact of COVID-19 on survivor’s health since the onset of COVID-19 infection”.

We have now added the following reference to the reference list section of the manuscript:

National Institute for Health and Care Excellence (NICE). 2020. [COVID-19 Rapid Guideline: Managing The Long-term Effects of COVID-19](#). [Accessed 3 March 2021].

Comment 14:

Line 38 “Outcome: The primary outcome was to measure the impact of COVID-19 on survivors and their partners and family members. Exposure: Person’s COVID-19 infection and its impact on partners and family members.”. Please change outcome to “the impact of COVID-19 on the quality of life of survivors and their partners and family members. Exposure: COVID-19 infection of participant or of the family member”.

Response:

Thank you for highlighting this inconsistency. We have now corrected it and replaced the text with the following, as suggested:

“Outcome: The impact of COVID-19 on the quality of life of survivors and their partners and family members.

Exposure: COVID-19 infection of the participant or of the family member.”

Reviewer: 2

(Dr. Himali Weerahandi, NYU Langone Health)

Comments to the Author:

Overall Comments:

Thank you for the opportunity to review this manuscript. This is an interesting, large, international cross-sectional study examining the impact of COVID-19 on QoL of survivors and their family members. I don’t think many studies have examined the impact COVID-19 has had on family members, so this is an important contribution. In addition, the researchers sought feedback from a patient and family members during survey development, which is to be commended.

Response:

Thank you for your appreciation.

I do have some questions for clarification regarding the survey methods and statistical analyses, which are detailed below.

Major Comments:

Methods:

Comment 1:

Is EQ-5D the same thing as EQ-5D 3 level? These terms seem to be used interchangeably throughout the manuscript, but it's not clear that they are referring to the same thing.

Response:

Thank you for highlighting this. We have now added the following to the Methods section of the manuscript:

"In this study, for simplicity throughout this manuscript, we refer to EQ-5D-3L as 'EQ-5D'."

Comment 2:

page 4, lines 56-59: "The study was only open to individuals who were diagnosed with COVID-19 and their family member or partner". How was COVID-19 diagnosis confirmed? If this was self-report only (without objective verification), this should be made clear.

Response:

Thank you for this very helpful suggestion. We have now added the following to the Methods section of the manuscript:

"The survey depended on the patient's self-report of the diagnosis of COVID-19 and did not specifically ask whether patients had had a COVID-19 positive test. However, further authentication of the diagnosis is given by both the patient and their relative having answered the survey."

Comment 3:

page 7, lines 48-53: "Section two was completed by the partner or a close family member of the survivor who provided basic demographic details and completed FROM-16." How did the investigators or the participant decide that a partner or close family member should fill out the survey? Did the family member have to be someone the patient lives with, or could be any close relation?

Response:

Thank you for your inquiry. In our survey, it was stated that 'Section 2 needs to be completed by a family member or partner'. We did not specify whether this should be someone the patient lives with or whether it could be any close relation; however in the survey the family member of the COVID-19 survivor was asked to specify their relationship to the patient. To clarify this further, we have now added the following to the Methods section of the manuscript:

"Section two was completed by the partner or a family member of the survivor who provided basic demographic details and completed FROM-16. The survey did not specify whether this should be someone the patient lives with or whether it could be any close relation; however, the family member of the COVID-19 survivor was asked to specify their relationship to the patient."

Comment 4:

page 8, line 34 specifies that the FROM-16 is available in several languages which contradicts the reasoning in the limitations section, "the study materials were available only in the English language"

Response:

Thank you for highlighting this point. Although FROM-16 is available in several languages, our full survey documents and the participant information sheet were only available in the English language. Participants could only take part if they could understand all of the documentation, not just FROM-16. We have now deleted 'the study materials were available only in the English language' in the limitation section of the survey and replaced it with the following:

"Although FROM-16 is available to researchers in several languages, our full survey documents and the participant information sheet were only available to the participants in the English language, and in the survey FROM-16 was also only provided in English. Participants could only take part if they could understand all of the documentation".

Comment 5

page 8, lines 38-40: "The primary outcome was to measure the impact of COVID-19 on survivors and their partners and family members." Please provide more details about the analyses. Was the dependent variable the total EQ-5D 3 level scores/ FROM-16 scores? Was the EQ-VAS score added to the EQ-5D 3 level score? Looking at Table 5, it seems that EQ-VAS is scored separately. While the Statistical analysis states, "Spearman's rank correlation coefficient and multiple regression analysis were conducted to understand the effect of independent variables (i.e. predictors) on the EQ-5D and FROM-16 outcomes," the investigators need to specify exactly what predictors were in these models (were they all the variables listed in Table 1? Or just the variables listed in Table 6? Did you decide what went into the model based on which correlations were significant? If so, this should be specified).

The investigators state "To determine differences between groups defined by each outcome chi-square tests (when appropriate, Fisher's exact tests) and Mann-Whitney U tests were computed".

Please provide more detail on what these group comparisons were. Were these bivariate comparisons based on patient/family member characteristics?

In Table 3 it looks like you reported bivariate outcomes on 3 patient characteristics (gender, pre-existing health condition, and hospitalisation). This is fine, but should be detailed in the methods section.

Response:

Thank you, please find our point-by-point response below:

Comment 5a:

Was the dependent variable the total EQ-5D 3 level scores/ FROM-16 scores? Was the EQ-VAS score added to the EQ-5D 3 level score? Looking at Table 5, it seems that EQ-VAS is scored separately.

Response:

Thank you for your comment. Both the EQ-5D-3L and the FROM-16 scores were treated in the analysis as dependent variables. As regards to EQ-VAS scores, they were calculated separately since it represents a different construct. We have now added the following to the statistical analysis section of the Methods:

"Both the EQ-5D-3L and the FROM-16 scores were treated in the analysis as dependent variables. The EQ-VAS score was calculated separately since it represents a different construct."

Comment 5b:

While the Statistical analysis states, "Spearman's rank correlation coefficient and multiple regression analysis were conducted to understand the effect of independent variables (i.e. predictors) on the EQ-5D and FROM-16 outcomes," the investigators need to specify exactly what predictors were in these models (were they all the variables listed in Table 1? Or just the variables listed in Table 6? Did you decide what went into the model based on which correlations were significant? If so, this should be specified).

Response:

Thank you for this helpful observation. The predictors included in the regression model are listed in Table 6 (not Table 1) and these were selected based on the, as yet, limited anecdotal evidence relating to COVID-19. We have now added the following text to the statistical analysis section of the Methods section of the manuscript:

"Spearman's rank correlation coefficient and multiple regression analysis were conducted to understand the effect of independent variables (i.e. predictors: survivor age, existing health condition, hospital stay

for COVID-19, weeks since first had COVID-19, survivor gender) on the EQ-5D outcomes. Similarly, these analyses were conducted to understand the effect of independent variables (EQ-5D score, age family member, weeks since first had COVID-19, family member gender, whether family member also had COVID-19, relationship to survivor, survivor age, survivor existing health condition, survivor hospital stay for COVID-19) on the FROM-16 outcomes”.

Comment 5c:

The investigators state “To determine differences between groups defined by each outcome chi-square tests (when appropriate, Fisher’s exact tests) and Mann-Whitney U tests were computed”.

Please provide more detail on what these group comparisons were. Were these bivariate comparisons based on patient/family member characteristics?

In Table 3 it looks like you reported bivariate outcomes on 3 patient characteristics (gender, pre-existing health condition, and hospitalisation). This is fine, but should be detailed in the methods section.

Response:

Thank you for this helpful comment. The group comparisons were carried out using bivariate analysis based on patient and family member’s characteristics. We have now added the following to the statistical analysis section of the Methods section of the manuscript:

“These bivariate comparisons were based on COVID-19 survivor’s characteristics (gender, existing health condition, and hospitalisation) and family member characteristics (gender and whether diagnosed with COVID-19)”

Comment 5d:

Also, a rationale as to why you chose to examine these characteristics over others that could also potentially have an effect on the score (such as age, occupation, etc).

Response:

Thank you for this observation. The study generated a vast amount of data and therefore, we had to be selective in our choice of predictors.

Comment 5e:

I do see that Table 5 reports correlations but it is unclear to me what this table is reporting. Is it the spearman correlation coefficient between EQ-5D and the other variables? If so, shouldn’t the spearman correlation coefficient be 1 for EQ-5D to itself?

Response:

Thank you for your helpful comment. Table 5 is a correlation matrix demonstrating the relationships between EQ-5D, FROM-16 and the participant demographics. In each row there is one cell with a dash. This denotes that a variable is being correlated with itself and has a value of 1. We agree that the spearman correlation coefficient be 1 for EQ-5D to itself and we have now replaced all dashes with 1 in Table 5. We have now altered the legend of Table 5 to the following:

“Table 5. Correlation matrix demonstrating the relationships between EQ-5D, FROM-16 and the participant demographics”.

Comment 6:

page 8, lines 38-40: “Covariates: The covariates included hospital stay due to COVID-19 infection, existing health condition of survivors, duration of COVID-19 infection”

If data about hospitalisation, existing conditions, duration of infection were reported by the patient, please make this clear. Self-reported data on hospitalisation and medical problems could be inaccurate and is a potential limitation. (see: Caraballo C, Khera R, Jones PG, et al. Rates and Predictors of Patient Underreporting of Hospitalizations During Follow-Up After Acute Myocardial Infarction: An Assessment From the TRIUMPH Study. Circ Cardiovasc Qual Outcomes 2020;13:e006231)

Response:

Thank you for this helpful comment. All covariate analysis was based on self-report. We have now mentioned in the Methods section and in the Limitations section of the Discussion that all covariate analysis was based on self-report. Thank you for the Caraballo et al. reference, which we have now added to the manuscript. We have now added the following to the Methods section of the manuscript:

“All the covariates, including hospitalisation, existing conditions and weeks since first had COVID-19 were based on self-report.”

We have added the following to the Limitations section of the Discussion:

“In addition, as all the covariates in the study were self-reported, data on hospitalisation and medical problems could be inaccurate and is a potential limitation (Caraballo et al., 2020).”

We have added the following reference to our reference list:

Caraballo C, Khera R, Jones PG, et al. Rates and Predictors of Patient Underreporting of Hospitalizations During Follow-Up After Acute Myocardial Infarction: An Assessment from the TRIUMPH Study. Circ Cardiovasc Qual Outcomes 2020;13: e006231

Results

Comment 7:

Similar to the Body Politic COVID-19 study (Hannah E. Davis, Gina S. Assaf, Lisa McCorkell, Hannah Wei, Ryan J. Low, Yochai Re'em, Signe Redfield, Jared P. Austin, Athena Akrami, Characterising Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact,” medRxiv 2020.12.24.20248802), the respondents are mostly women—it’s worth noting with respect to generalizability of the findings because men are more likely to be admitted to the hospital for COVID-19. I also wish race data was collected, particularly given the disproportionate effect COVID-19 has had on immigrant and BIPOC communities.

Response:

Please find below our point-by-point response.

Comment 7a:

Similar to the Body Politic COVID-19 study (Hannah E. Davis, Gina S. Assaf, Lisa McCorkell, Hannah Wei, Ryan J. Low, Yochai Re'em, Signe Redfield, Jared P. Austin, Athena Akrami, Characterising Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact,” medRxiv 2020.12.24.20248802), the respondents are mostly women—it’s worth noting with respect to generalizability of the findings because men are more likely to be admitted to the hospital for COVID-19.

Response:

Thank you for this comment concerning the fact that patient respondents were mostly women. This is of interest, especially as it is reported that men are more severely impacted by COVID-19 than women. We agree that this may dilute the generalisability of the results, and this is already mentioned in the Limitations section of the Discussion. However, the majority of social media COVID-19 support groups

were started by women who had COVID-19 and hence attracted more female attention. Women, in general, tend to have a more caring attitude and are ready to share their experiences to help and support others. This could be the reason why women responded more. Another reason could be that women may have suffered post-COVID symptoms more than men and hence were more interested in the survey to raise awareness about it. We have therefore added the following text to the Discussion section of the manuscript:

“Interestingly of the patients who participated, most (76.6%) were women, as found in other surveys (Davis et al. 2020); however, there was a higher proportion of men among participating family members (66.5%). This may be because the majority of COVID-19 social media support groups have been initiated by women (patients), and the most convenient family person to ask to participate might be their partners (mostly male)”.

We have now added the following reference that you have provided to the reference list of the manuscript:

Hannah E. Davis, Gina S. Assaf, Lisa McCorkell, Hannah Wei, Ryan J. Low, Yochai Re'em, Signe Redfield, Jared P. Austin, Athena Akrami, Characterising Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact,” medRxiv 2020.12.24.20248802

Comment 7b:

I also wish race data was collected, particularly given the disproportionate effect COVID-19 has had on immigrant and BIPOC communities.

Response:

Thank you, we agree this is a very important point. There were two reasons for not including the issue of race in this study: 1) lack of clarity on the definition of different racial and ethnic groups and its general understanding and applicability globally; 2) when this study was planned, there was at that time little indication that racial factors might influence prognosis of COVID-19. Given the importance of this issue, we feel that to do the whole topic justice, this topic should be considered as a single focus of possible future studies.

Comment 8:

page 12, line 26-31, “There was a significant gender difference for ‘mobility’ and for ‘pain and discomfort’ ($p \leq 0.05$) with females being more impacted than males (Fig 1).” However, Figure 1 does not report gender differences. Do you mean Table 3

Response:

Thank you for this helpful observation. We apologise for this oversight, we did mean Table 3. We have now corrected this in the Results section of the manuscript, and it reads as follows:

“There was a significant gender difference for ‘mobility’ and for ‘pain and discomfort’ ($p \leq 0.05$) with females being more impacted than males (Table 3)”.

Comment 9a:

page 16, lines 24-27: “There was a significant positive association between the family members’ FROM-16 scores and the survivors’ EQ-5D scores ($p < 0.001$) (Fig 4)” I think you are referring to the figure that is labeled as figure 3.

Response:

Thank you for this helpful observation. We apologise for this oversight, we did mean Figure 3. However, Figure 3 does not offer more information than what has already been included in Table 5, and therefore, we have now removed Figure 3 from the revised manuscript.

We have now corrected this in the Result section of the manuscript, and it reads as follows:

“There was a significant positive association between the family members’ FROM-16 scores and the survivors’ EQ-5D scores ($p < 0.001$) (Tables 5 and 7)”.

Comment 9b:

Could you provide details on how you established that this is a positive correlation between these scores? Is it based on the spearman’s correlation coefficient reported in Table 5?

Response:

Thank you for your comment. The scoring of FROM-16 is based on a score of ‘0’, meaning normal quality of life and the maximum score of ‘32’ meaning the most severely impacted quality of life. Similarly, the scoring of the questions of the EQ-5D is based on a score of ‘0’, meaning no impact and a high score indicating the most severely affected quality of life. Therefore, we used the descriptor ‘positive correlation’ to indicate to the reader that not only was there an association between the two but also to demonstrate that the extent of the impact on family quality of life and on patient quality of life run in the same direction.

You are correct that a positive correlation is based on the spearman’s correlation coefficient reported in Table 5.

Comment 9c:

The data you have displayed in the Figure does not look convincing that there is a positive relationship (despite the diagonal line drawn---how was this line calculated?), and in fact looks fairly spread out evenly.

Response:

Thank you for this Comment. We agree that Figure 3 does not offer more information than what has already been included in Table 5, and therefore, we have now removed Figure 3 from the revised manuscript.

Comment 10:

page 16, lines 33-41: “However, other variables such as hospital stay, existing health condition, number of weeks since COVID-19, survivors’ age and gender indicated that being female or being older was associated with lower EQVAS scores ($p < 0.05$), that is lower health status.”

I’m confused as I thought you were reporting correlations between EQ-5D and the other characteristics, and not between EQVAS and the patient/family member characteristics.

Response:

Thank you for your Comment. We are sorry for this confusion. This section of the results talks about the correlation of the EQ-5D, EQ-VAS and FROM-16 to all variables. The previous paragraph discussed EQ-5D and FROM-16 correlation with other variables. That is followed by another paragraph that focuses on EQ-5D VAS and which starts with the following sentence “The EQ-VAS scores showed a significant inverse relationship with EQ-5D ($p < 0.01$)”. The section that you quote continues to discuss EQ-VAS

relationships with other variables. We apologise for mistakenly including age and number of weeks since COVID-19 in this list. The revised sentence now reads as follows:

“The EQ-VAS scores showed a significant inverse relationship with EQ-5D ($p < 0.01$). However, other variables such as hospital stay, existing health condition and gender (being female) were associated with lower EQ-VAS scores ($p < 0.05$), that is, lower health status”.

Tables

Comment 11:

Table 5: please explain what the 1-10 in the top column means.

Response:

Thank you for your comment. We have now added the following descriptor as a footnote to Table 5.

“The numbers 1-10 in the horizontal heading bar represent the same numbers as given in the left-hand column. Each number refers to the variable described next to it”.

Comment 12:

Tables 6 and 7: Please specify which gender was the reference for the multivariable analyses.

Response

Thank you for this helpful Comment. The gender specifications for Tables 6 and 7 were as follows males=1, and females=0. Females are the reference group. We have now clarified this by adding a footnote to Tables 6 and 7:

“Males=1 and females =0; females are the reference group.”

Discussion

Comment 13:

page 20, lines 35-41: “Survivors with existing health conditions did not differ significantly from those without such conditions except for mobility. and having an existing health condition was not a significant predictor of impact on the family member/partner’s QoL.”

I would temper this statement as existing health conditions were self-reported and also all medical problems were lumped together---patients with just hyperlipidemia are likely to be different from a patient with more serious medical conditions (such as heart failure).

Response:

Thank you for your Comment. We agree that existing health conditions were self-reported by respondents and the severity of the existing health condition was not reported. We therefore have replaced this text with the following:

“Although existing health conditions were self-reported and severity was not stated, survivors with existing health conditions did not appear to differ from those without such conditions except for mobility. Having an existing health condition was not a clear predictor of impact on the family member/partner’s QoL.”

Comment 14:

Additional limitations for study include that it does not follow a pre-specified cohort, rather patients opt in to report their symptoms. People who are experiencing symptoms may be more likely to participate in a study such as this versus those who have gotten completely better and moved on with their lives.

Response:

Thank you for your Comment. We agree that this may have led to selection bias. We have added the following sentence to the Limitations section of the Discussion as follows:

“It is also possible that people who experienced persisting symptoms may have been more likely to have participated in the study”.

Introduction

Comment 15:

page 3-4 lines 57-60: This sentence about the FROM-16 and explaining its suitability for this study would fit better in the Methods section rather than the Introduction section.

Response:

Thank you for this helpful Comment. We agree with your suggestion and have now moved this sentence to the Methods section of the manuscript.

Minor Comments

Tables

Comment 16:

Table 1: would report interquartile range to correspond with median fore age and duration of COVID-19 symptoms. You report the full range, which is interesting, but the IQR usually is also reported.

Response:

Thank you for your Comment. We apologise for having omitted this from Table 1 and have now added the interquartile range of the two variables.

Comment 17:

Table 1: occupation, for the group that is in paid work, would be interesting to know if these participants work from home (I know that's not possible at this time to collect that data, but just food for thought).

Response:

Thank you for this interesting thought; unfortunately, we did not collect such data.

VERSION 2 – REVIEW

REVIEWER	Himali Weerahandi NYU Langone Health
REVIEW RETURNED	12-Apr-2021

GENERAL COMMENTS	Overall, I think the authors have adequately addressed the
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	<p>reviewers' concerns. I do have a few minor comments:</p> <p>Methods I now understand you calculated spearman's rank correlations to examine relationships between EQ-5D, FROM-16, and EQ-VAS with the other scores and patient demographics, and this is reflected in Table 5. I do think it could be made a little clearer in the Methods that EQ-VAS is a separate outcome for your study. One suggestion could be to change the sentence "The EQ-VAS score was calculated separately since it represents a different construct" to "The EQ-VAS component of EQ-5D was examined separately as a dependent variable."</p> <p>Other comments: - Page 6 "...weeks since first had COVID-19": would change this to "number of weeks since COVID-19 diagnosis". - Table 5: To increase clarity of this table, I suggest replacing the numbers in horizontal heading bar with the actual variable name. - Table 6: To increase clarity of this table, I suggest "Survivor gender" with "Male gender". Same with Table 7, I suggest replacing "Family member gender" with "Male Family Member"</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

(Dr. Himali Weerahandi, NYU Langone Health)

Comments to the Author:

Overall Comments:

a) *Overall, I think the authors have adequately addressed the reviewers' concerns.*

Response:

We thank the reviewer for her encouraging comment and are pleased that our responses have been satisfactory.

Comment

b) *I do have a few minor comments*

Response:

Thank you. We have addressed all of your minor comments below.

Comment 1:

Methods:

I now understand you calculated spearman's rank correlations to examine relationships between EQ-5D, FROM-16, and EQ-VAS with the other scores and patient demographics, and this is reflected in Table 5. I do think it could be made a little clearer in the Methods that EQ-VAS is a separate outcome for your study. One suggestion could be to change the sentence "The EQ-VAS score was calculated separately since it represents a different construct" to "The EQ-VAS component of EQ-5D was examined separately as a dependent variable."

Response:

Thank you for this very helpful suggestion. We have now replaced the text “The EQ-VAS score was calculated separately since it represents a different construct” in the Methods section of the manuscript with the following text:

“The EQ-VAS component of EQ-5D was examined separately as a dependent variable.”

Other comments

Comment 2:

Page 6 “...weeks since first had COVID-19”: would change this to “number of weeks since COVID-19 diagnosis”

Response:

Thank you for this suggestion. We have now replaced the text “...weeks since first had COVID-19” on page 6 in the Methods section of the manuscript with following text :

“...number of weeks since COVID-19 diagnosis”

We have also replaced the text “...weeks since first had COVID-19” with “...number of weeks since COVID-19 diagnosis” throughout the manuscript.

Comment 3:

Table 5: To increase clarity of this table, I suggest replacing the numbers in horizontal heading bar with the actual variable name.

Response:

Thank you very much for your suggestion. We have now replaced the numbers in the horizontal heading bar in Table 5 with the actual variable names.

Comment 4:

Table 6: To increase clarity of this table, I suggest “Survivor gender” with “Male gender”. Same with Table 7, I suggest replacing “Family member gender” with “Male Family Member”

Response:

Thank you for this very helpful comment. We have now replaced “Survivor gender” with “Male gender” in Table 6 and replaced “Family member gender” with “Male Family member” in Table 7

Thank you for considering this manuscript for publication.