

## Peer Review File

Article information: <https://dx.doi.org/10.21037/apm-22-1304>

### Reviewer A

#### General comments

Comment 1: My advice is to have your manuscript checked by a native speaker. Besides numerous grammatical errors, I miss some fluency in the text, making it hard to read at times. I have tried to highlight all the grammar mistakes, but I'm not a native English speaker so I guess there'll be more. The lack of fluency is especially true for the quotes.

Reply 1: Thank you for the advice. A native speaker and an international member of our research team checked the manuscript for grammar and fluency.

Changes in the text: Throughout the manuscript.

#### Title and abstract

Comment 2: "A vicious cycle of breathlessness-panic-breathlessness leads to emergencies." I would rephrase this, 'emergencies' is very vague.

Reply 2: Thank you for the comment, we revised the sentence.

Changes in the text: page 4, line 67

Comment 3: "There was a significant indirect effect of episodic breathlessness' intensity on experienced panic in an episode mediated by catastrophizing thoughts regarding breathlessness." I struggle with this sentence, it's difficult to understand. Plus: How certain is this 'significant indirect effect'?

Reply 3: Thank you for this comment. Please compare our response with comment 27. Both unstandardised coefficients for [episodic breathlessness' intensity] -> [catastrophizing thoughts regarding breathlessness] (a) and [catastrophizing thoughts regarding breathlessness (also with [episodic breathlessness' intensity] in the model) -> [experienced panic] (b) were statistical significant. Thus, we conclude that mediation was present (and statistical significant).

Comment 4: Some comma's in the conclusion of your abstract might improve readability.

Reply 4: Thank you for your advice, we added commas and think it improves the readability (see page 4, lines 97, 98)

Changes in the text: page 5, lines 99,100

#### Introduction

Comment 5: Leads to (115) might be a bit too strong. I suggest: may lead to

Reply 5: Thank you we revised the sentence in the manuscript.

Changes in the text: page 7, line 113

Comment 6: can be continuous or episodic, respectively □ I suggest: can be either continuous or episodic.

Reply 6: Thank you, we modified the text as suggested.

Changes in the text: page 7, 114

Comment 7: Symptoms (118): psychological symptoms

Reply 7: Thank you, we revised the text as suggested.

Changes in the text: page 7, 125

Comment 8: Vice versa it has been found (134): please rephrase this sentence. (For example: Conversely, ...)

Reply 8: Thank you we revised the sentence in the manuscript.

Changes in the text: page 7, line 130

Comment 9: The sentence in 140-142 is both grammatically incorrect and unclear.

Reply 9: Thank you for your comment. We rephrased the sentence: As qualitative studies indicate, anxiety/panic triggers breathless episodes,[10] and panic is a consequence of a breathlessness episode.[23]

Changes in the text: page 7/8, lines 136-150

Comment 10: 145-146: Although there is some research on patients' experiences with panic and breathlessness, as well as its treatments...

I don't think it's fair to say there is 'some research'. Furthermore, I miss references on CBT in breathlessness, for example, doi:10.1183/23120541.00094-2018. doi:10.1016/j.resp.2015.05.013. Doi:10.1183/09031936.00060309.

Reply: Thank you for the advice, we revised the text and included the references on CBT as suggested.

Changes in the text: page 8, 153-155

Comment 11: 151: what is meant with 'high burden'? Many patients, or the burden of disease those patients experience?

Reply 11: With 'high burden' the burden of the breathless episodes those patients experience is meant. We modified the text accordingly.

Changes in the text: page 8, line 160

## **Material and methods**

Comment 12: Can you describe more clearly (first sentence) how you recruited the participants? You write: 'the sample of the cross-sectional study', but the word sample implies that part of the enrolled patients for CoBeMeb were included.

Reply 12: Thank you for the comment. That was a misunderstanding, all patients of the CoBeMEB study also filled out the questionnaires for the present study. I corrected the sentence.

Changes in the text: page 8, line 170-172

Comment 13:165: Data was □ data were  
Reply 13: Thank you we revised it accordingly.  
Changes in the text: page 8, line 173

Comment 14: Study procedure: were the questionnaires self-report? This is unclear.  
Reply 14: We used self-report questionnaires, and we revised them accordingly.  
Changes in the text: page 9, line 202

Comment 15: Measures: is PHQ a self-report questionnaire?  
Reply 15: Yes, the PHQ is a self-report questionnaire.  
Changes in the text: no changes in the text, as we only used self-report questionnaires.  
We describe this on page 9, line 202 (see comment above)

Comment 16: 190-191: to me, the difference between panic disorder and panic syndrome is unclear. Since your article aims at clinicians working with end stage respiratory disease, some clarification is justified.  
Reply 16: Thank you for the comment. We revised the sentence for clarification.  
Changes in the text: Page 9, lines 212-219

Comment 17: 195: what were these self-developed questions?  
Reply 17: Thank you for the question. We present them in Supplement 1.  
Changes in the text: none, but new file 'Supplement 1'

Comment 18: 198: 10=extreme panicky, extremely. I wonder if 'panicky' is the right term to use here.  
Reply 18: Thank you for the advice. We modified it as suggested. We assume that panicky and panic are both right, but as panic is more common we revised it.  
Changes in the text: page 10, line 254

Comment 19: 200: experienced in a situation, in which they feel □ past and present within one sentence  
Reply: 19: Thank you, we revised it as suggested.  
Changes in the text: page 10, line 256

Comment 20: 222: panic, episodic breathlessness, episodic breathlessness, and panic. This is unclear for the reader (A, B, B, A.)  
Reply 20: Thank you for the comment, it should be clearer to understand.  
Changes in the text: page 10, line 275

## Results.

Comment 21: 230: I'm not sure one 'answers' the SCID  
Reply: 21: We modified it, please see the changes in the text.

Changes in the text: page 11, line 297

Comment 22: 237: multiple responses possible, for further descriptions of patients' sociodemographics and clinical data, see the corresponding paper (27). I suggest a new sentence starts here, with more clarity on the multiple responses (to which questions?)

Reply 22: Thanks for the advice. We revised the sentence for clarity.

Changes in the text: page 11, lines 302-304

Comment 23: 243: Patients rated their general feeling of being panicky ( $M=3.38$ ;  $SD=2.7$ ). I don't understand this sentence.

Reply 23: We revised the sentence and it should be clearer to understand.

Changes in the text: page 11, line 310

Comment 24: 252: Feelings?

Reply 24: Modified as suggested.

Changes in the text: page 12, line 335

Comment 25: 274-276: please rephrase and/or use some comma's for clarity.

Reply 25: We rephrased the sentence for more clarity.

Changes in the text: page 13, lines 368-370

Comment 26: 287: how do you define high scores? Are those the 'high anxiety sensitive patients' (294?)

Reply 26: Thank you for the question. High scores on the BCS are those scores higher than 30. Patients with high scores on the BCS are not necessarily the same patients as the persons scoring high on the ASI, here described as 'high anxiety sensitive patients'. Groups of patients with high/low scores on the ASI and BCS were defined following recommendations from the literature (see section 'data analysis'). We modified the sentences for clarity.

Changes in the text: page 13, lines 380 and 386

Comment 27:291: are you sure mediation analysis can show a significant, yet indirect effect?

Reply 27: Thank you for this comment. In a mediation analysis as proposed by [Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol.* 1986 Dec;51(6):1173-82. doi: 10.1037//0022-3514.51.6.1173. PMID: 3806354] both unstandardised coefficients whose product equals the indirect effect were statistically significant at level 0.05. Thus, we conclude that mediation was present (and statistically significant).

**Discussion.**

Comment 28: 302-304: The great majority of the patients differed in the frequency and duration of panic when suffering from a breathlessness episode.

Isn't this self-evident? It would surprise me if all had the same duration and frequency. However, it is written down as if this is an important finding. I would be more interested in the range of duration (e.g. between 5 and 30 minutes).

Reply 28: Thank you for the question. We did not assess the duration of the panic experience within a breathlessness episode. We think that the fact that the duration of panic during a breathlessness episode differs is interesting as some patients manage to avoid experiencing panic at all/ during the whole episode. The mechanisms of how they succeed to reduce the panic need to be investigated.

Changes in the text: page 14, line 415-419

Comment 29: 304: Still, a few patients never suffered from panic when having a breathlessness

episode. This is self-evident too, you stated that most patients experienced panic, so some didn't.

Reply 29: Please see comment/reply 28.

Comment 30: 305: panic-spectrum pathology: this term wasn't used in the results section and is therefore confusing (to me).

Reply 30: Thank you for the comment. 'Panic-spectrum pathology' is the title of a section in the results part summarizing the results of the PHQ, SCID, and panic question.

Changes in the text: none.

Comment 31: 310, 'and thus reduce the burden', I would omit this last part of the sentence. It is what we strive to do, naturally, but we cannot be sure of this.

Reply 31: Thank you, revised as suggested.

Changes in the text: page 14, lines 424

Comment 32 317: both, the – omit comma.

Reply 32: Thank you, revised as suggested.

Changes in the text: page 14, line 429

Comment 33: 319: but also managing

Reply 33: Thank you, revised as suggested.

Changes in the text: page 14, line 431

Comment 34: 323-325: please rephrase for clarity

Reply 34: Thank you, we rephrased the sentence.

Changes in the text: page 14, lines 434-436

Comment 35: 326: do not experience panic or managed – past and presence in one sentence.

Reply 35: Thank you, we corrected the sentence.

Changes in the text: page 14, line 436

Comment 36-39:

327: I wouldn't say 'two patients', rather 'a very small minority'

328: omit 'this'

329: are these factors or patterns? Frightening panic: is it ever not frightening?

331: 'up to': please rephrase

Reply 36-39: Thank you for the advice. We modified the sentences accordingly.

Changes in the text: page 14/15, lines 437-491

Comment 40: 333: play an important role in predicting panic: please rephrase

Reply 40: We rephrased the sentence, thank you for the comment.

Changes in the text: page 15, line 492

Comment 41: 335: 'the symptoms': which?

Reply: 41: Thank you for the question. We mean the symptoms that usually accompany panic in any context vs. during a breathlessness episode. We revised the sentence for clarity.

Changes in the text: page 15, line 494

Comment 42: 335: When patients were asked to indicate the symptoms, they usually suffer from when experiencing panic in any context vs. experiencing panic during a breathlessness episode, it was remarkable, that 8/11 symptoms differed significantly. Please rewrite this sentence, it is grammatically wrong and unclear.

Reply 42: We rephrased the sentence.

Changes in the text: page 15, lines 494-501

Comment 43: 338: what is meant by a 'statistically measurable difference' ? Plus, "the difference between a general panic moment and panic in an episode" : please clarify what the difference is and why this is important.

Reply 43: We found a significant difference between the occurrence of the symptoms when people were suffering from a breathlessness episode vs. outside the context of a breathlessness episode. We rephrased the sentence for clarity.

Changes in the text: see comment 43

Comment 44: 342: please define the high-scorers

Reply 44: Thank you for the advice. We defined the high-scorers in the results section, as suggested in comment 26 (see page 12, lines 280 and 287)

Changes in the text: none

Comment 45: 360: the model focusses

Plus: it would be interesting to elaborate on clinical utility the BTF model. In my opinion, the most powerful part of this model is the explanation that anxiety leads to rapid, shallow

breathing, resulting in an increase in hyperinflation (in the case of COPD) and thus, worsening of the symptom

Reply 45: Many thanks for your comment. We agree that the BTF model has several aspects which help in clinical practice to discuss with the patient (and their carers) the different influencing effects (e.g. emotions, thoughts, breathing techniques, etc.) on their breathing. Our results support this.

Changes in the text: page 16, line 574

Comment 46: 377: Here, it would be interesting to mention the hypothesis, that breathlessness catastrophizing thoughts are related to PTSS (post-traumatic stress syndrome). This might explain why patients usually have anxiety for breathing related situations. See reference <https://pubmed.ncbi.nlm.nih.gov/36451139/> and <https://pubmed.ncbi.nlm.nih.gov/24983958/>

Reply 46: Thank you for this interesting discussion. As we did not assess anything regarding PTSS we are a bit reluctant to take part in this discussion with our results. In addition, the experience of one or several exacerbations of COPD is complex and more than breathlessness only (although this is an important part of it). The paper describes a correlation between exacerbations and PTSS but could not determine breathlessness as the determinant factor. However, a very interesting hypothesis that is worth further investigation.

Comment 47 and 48

387: can □ may (2x)

388: judge: interpret

Reply 47 and 48: Thank you, revised as suggested.

Changes in the text: page 17, 612-613

Comment 49: 396: please rephrase 'being panicked'

Reply 49: We rephrased the expression.

Changes in the text: page 17, line 621

Comment 50: 410: This is a solid sample given the vulnerability of patients suffering from life-limiting diseases: Although patients are vulnerable, this cannot be used as an excuse to include enough patients.

Reply 50: We modified the sentence.

Changes in the text: page 17, lines 633-636

Comment 51: 415: the □ a

Reply 51: Thank you, revised as suggested.

Changes in the text: page 18, line 674

Comment 52: 432: see comment line 327

Reply 52: We modified our text as advised.

Changes in the text: page 18, line 689

Comment 53: Table 3: please have the quotations translated by a native speaker. It seems as if they have been translated by Google. Some errors:

- That also goes from one second to the next
- Afterward instead of afterwards
- The shot can also backfire (?)

Plus I wouldn't use capitals but italics for emphasis

Reply 53: We asked a native speaker to check and translate the quotations.

Changes in the text: Please see Table 3

### **Reviewer B**

This study investigates the links between breathlessness and panic in 46 people living with COPD. The study is well designed and collects a variety of information regarding the nature and frequency of episodic breathing and panic attacks in the recruited cohort. The limits of a small sample size are discussed. The data is analysed fully and presented appropriately. The conclusions are supported by the data presented. An interesting and worthy study.

Comment 54: Minor point: Line 281, page 6, Is a fear of dying, classified as being immediately or a general fear, or both.

Reply 54: Thank you for your comment. It refers to the fear of dying during a panic attack, so I would assume it is an immediate fear of dying. We revised the sentence accordingly.

Changes in text: page 13, line 374

### **Reviewer C**

Thank you for presenting this paper that set out to better the understanding of the interaction between panic and episodic breathlessness to develop appropriate support for patients suffering from this symptom.

This is an important area for research and the exploratory data and topic are of interest to those working in this field. The feedback below offers opportunity to consider areas where the manuscript can be further strengthened.

Comment 55: The methodological approach is unclear. It is presented as a cross sectional study but you are presenting qualitative data as well therefore this is a mixed methods study. The STROBE guidelines only ensure the reporting of the quantitative data and NOT the qualitative data. Suggest that you revise title and methods to clarify it is mixed methods if you are including the qualitative data.



Reply 55: Thank you for the advice. The aim of the paper was a description of the interaction between panic and episodic breathlessness, using quantitative data. As we asked the patients one additional open-ended question, we decided to mention it in the paper as it allows a better understanding of the interaction between panic and episodic breathlessness. We think the presentation of the paper as a mixed-methods study could be misleading because nearly all data are quantitative and we see the open-ended question as only additional information. We think the description of qualitative data/qualitative interview was confusing for the one open-ended question we asked, so we changed it in the manuscript.

Changes in the text: We corrected it throughout the manuscript.

Comment 56: Reference to guidelines for reporting mixed methods or qualitative data (COREQ) is necessary to improve the reporting standard of the qualitative methods, analysis and findings of the interviews. e.g. Who conducted the interviews? How long did the interviews last for? Were they all conducted individually? What is the researcher's experience of qualitative research, reflexivity? How did you sample the 22 people interviewed from the total n=46. Any details on the interviewees? Topic guide for interviews, were they semi-structured? Data saturation? Further quotes to illustrate the themes would also help. The inclusion of further qualitative details also helps address the balance of the paper and reflects the importance of this data which you note.

Reply 56: Thank you for the important question. We realized that our wording (e.g., qualitative interview) was misleading for the qualitative data we assessed. We recorded the answers to the open-ended question. While the information we gained thanks to the answers is very interesting, they do not have the comprehensiveness of a qualitative interview. For this reason, we revised the manuscript accordingly.

Changes in the text: Changes throughout the manuscript.

Comment 57: Please can you also add more details to the content analysis process as there are very few details on the inductive coding and data analysis.

Reply 57: Thank you for the comment. We discussed it with the research team and have concluded that, given the focus of the paper, which is to supplement and deepen quantitative data with qualitative responses, we believe the description of the methodology is appropriate in this way.

Comment 58: Please can you justify the sample size for the inferential statistics? Is it worth doing anything other than descriptive statistics with n=46, although I note you have stated exploratory data analysis, page 4, but I think it needs to be much more explicit and stated earlier in the paper in the abstract and the methods that this is exploratory work given the sample size.

Reply 58: Thank you for the advice. We totally agree and stated earlier in the manuscript that we present exploratory work.

Changes in the text: page 4, lines 81/82, page 9, lines 219-220

Comment 59: The introduction does not clearly explain chronic breathlessness in terms of recent research and how does episodic breathlessness relate to acute on chronic breathlessness? It would be helpful to include more up to date references and reflect on the current thinking citing the work by Johnson MJ, ERJ, 2017 chronic breathlessness syndrome and Hutchinson A, JPSM, 2019. Please could you explain what the relationship is between continuous/ episodic breathlessness and chronic/ acute on chronic breathlessness and how do these different concepts fit together?

Reply 59: Many thanks for this discussion. It is a very interesting and still ongoing discussion about which terms are best describing what we are talking about and what the patient experiences. It is a bit confusing that so many different terms are used in research nowadays (e.g. dyspnea crisis, episodic breathlessness, acute on chronic, etc.) although much overlap exists and it might be that different terms are used for the same phenomenon or experience. Therefore, it would be good to see a bring-together expert consensus process reducing the number of terms and consent one or two. However, this is beyond the scope of this study and paper and its introduction. For this, we refer to the definition of international experts of episodic breathlessness and we used this definition for this paper.

Comment 60: The quantitative data is at baseline then the qualitative data is collected 6 weeks after the delivery of the cognitive behavioural intervention for the management of episodic breathlessness so did participant's views of panic change and what is the impact of the intervention on the interview data? It may be worth acknowledging the influence of the intervention on the qualitative data given that you describe that participants benefited from the intervention due to reduced panic in an episode of breathlessness.

Reply 60: Thank you for the advice and questions. We adjusted the manuscript, acknowledging the potential impact of the intervention on the answers given after the intervention.

Changes in the text: page 17, lines 638-673

**Minor changes/rewording to consider:**

Comment 61: Limitations: - what do you mean by solid sample? Please consider changing the word "solid".

Reply 61: Thank you for the comment, we rephrased the sentence for clarity.

Changes in the text: page 17, line 633

Comment 62: Do themes "emerge"? Please consider changing to say themes generated

Reply 62: We modified our text as advised.

Changes in the text: page 12, line 350