Author’s response to reviews

Title: Circadian rhythm of COPD symptoms in clinically based phenotypes. Results from the STORICO Italian observational study.

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Ulrich Koehler (Reviewer 1):

This is a very interesting and well-done study in patients with clinically defined phenotypes of COPD. The circadian rhythm of respiratory symptoms is analyzed. As main results the authors find that the majority of early-morning and day-time symptoms are found in patients with chronic bronchitis (CB) and emphysema (EM). Nighttime symptoms were more prominent in patients with CB.

First, definition of clinical phenotypes of patients with COPD is very senseful, however it may be difficult sometimes. What is your experience?

Answer: We would like to thank the Reviewer for sharing these thoughts. There is no doubt that in selected patients it is problematic to find a clinical phenotype perfectly fitting the traditional definitions. We have no figures on this grey zone, but our opinion is that at least 10-15% of
COPD patients fall in, and more if we deal with elderly people. Indeed, the awareness of this methodological problem is founding an ongoing alternative classificatory approach to the COPD patients enrolled in the STORICO study. Meanwhile, the analysis of circadian rhythm of symptoms adds to our awareness of disease heterogeneity and variant clinical presentations.

The following questions are of interest:

1. Frequency of nocturnal symptoms is heightened in patients with CB. Your explanation for this is supine position, bronchial hypersecretion and accumulation of mucus.

   How many of your patients with CB/EM and nocturnal symptoms did still smoke? Did you compare those patients with and without still existing nicotinism?

   Productive cough being strongest during sleep and morning hours is highly suggestive of still smoking. It is very likely that continued tobacco exposure leads to more productive cough and respiratory symptoms by progressive airway inflammation.

   Answer: We thank the Reviewer for the comment. Upon your suggestion, we evaluated the frequency of current smokers suffering from night-time symptoms in CB vs EM patients and we calculated the Chi-square test of smoke vs clinical phenotype. There was no association between the two variables: in other words, considering patients with night-time symptoms, the frequency of current smokers was not significantly higher in CB than in EM patients; this novel finding was added in the Results Section (see lines 268-270). In addition, we calculated the prevalence of current smokers in each phenotype both in symptomatic and asymptomatic patients, and added this information in the revised version of the text (see lines 270-273).

   It cannot be excluded that the type of respiratory symptoms to some extent accounts for a more precise reporting in CB than in EM patients, given that cough is an easily recognized cause on nocturnal awakenings. On the other hand, it is likely that awakening related to dyspnea is to some extent misinterpreted as due to nicturia related to the increase in abdominal pressure. This hypothesis is supported by the misinterpretation of nocturnal awakening in elderly OSA patients. Finally, it is conceivable that nighttime rest prevents many EM patients from reaching the threshold for dyspnea. Thus, a mix of causes is likely to variably account for the lesser prevalence of nocturnal symptoms in EM patients, although we may only speculate on it (see lines 365-372).

2. In the discussion I miss the opportunity of ambulant monitoring of respiratory symptoms like cough. Especially during night-time and the early-morning hours it would be possible to monitor cough and wheezing objectively because of less artifacts. Longterm recording offers a promising opportunity in the objective assessment of respiratory symptoms.
Answer: The Reviewer is right. Indeed, continuous objective monitoring of symptoms would be of great value in clinical practice. Unfortunately, at the time of designing the STORICO study we did not consider the opportunity of objective recordings through dedicated tools. We have added some speculation on this topic in the Discussion section with proper references (see lines 381-383).

3. Definition of clinical phenotypes is of prognostic value. What does this mean? What are the consequences for you? Changing or intensifying medication?

Answer: The Reviewer correctly underscores an important topic, that is, the prognostic consequences of clinical phenotypes. As discussed in the original version of the paper, advocating a more aggressive pharmacological approach or, alternatively, including non pharmacological treatments, such as rehabilitation or non invasive ventilation are potential important actions. We have reformulated this paragraph to better describe the consequences of the identification and description of different clinical phenotypes (see lines 350-357).

Marise J. Kasteleyn, PhD (Reviewer 2):

General:

Interesting topic. However, the main outcome/research question is not so clear.

The methods should be rewritten so that the primary aim is more clear, and methods including analyses should be in line with that aim.

Answer: We deeply thank the Reviewer for the precious suggestion. We clarified the aim in the “Background” paragraph (highlighting primary and secondary objectives of the paper) (see rows 103-113) and changed the “Methods” paragraph consistently (see rows 213-233).

Also, since many tests are performed it is difficult to distinguish main and side issues.

Answer: The “Methods” paragraph was changed to clarify the purpose of the tests (see rows 224-233).

Also, in the discussion all those secondary tests are not discussed, so for me it is not clear what the added value of these analyses is.
Answer: We originally focused the discussion on the “core information”, i.e. on that provided by tests having greater classificatory potential. However, we acknowledge that also negative results carry important information. Accordingly, they have been briefly discussed (see rows 373-392).

Also, there are several language errors, so an English check is recommended.

Answer: a revision of the manuscript by a mother tongue English was performed.

Introduction:

- Recent interesting ACOS study definition

Answer: We thank the Reviewer for suggesting this reference. The paper compares registry-based and self-reported ACOS definitions, and concludes that consensus about ACOS definition in different care settings is urgently needed. We have already stated that controversies in terms of ACO definition exist, and we have added the suggested reference in the revised version of the text (see row 84-86).

- Rationale for evaluating circadian rhythm is missing. And why do you expect differences between those phenotypes regarding the circadian rhythm.

Answer: We have modified the text to highlight that the primary aim was to investigate the circadian rhythm of respiratory symptoms in the different clinical phenotypes. The current study was designed on the basis of previous findings from the ASSESS study, which had shown that the circadian variability of symptoms worsens quality of life and affects patient reported outcomes.

We cited ASSESS study in Discussion at rows 317-322.

We therefore aimed to dissect this phenomenon by assessing whether and to which extent the circadian variability of symptoms characterizes a specific clinical phenotype. At the time of study design and conduction we were not able to predict any difference among the different clinical presentations, except for a stricter dependence of dyspnea (phenotype EM) from physical effort and, as a consequence, a higher daytime prevalence of this symptom.

- "whereas" seems the wrong word in line 42, it is not in contrast with the statement before the comma.
Answer: The word “whereas” was deleted (see row 50)

- Results that are reported in abstract are not reported in body of article (eg regarding CM patients being more commonly overweight etc). Focus should be on main findings in abstract.

Answer: We thank the Reviewer for raising this point. The content of the Abstract was changed and aligned accordingly to the content of the body of the article (see rows 31-37 and 50-58). In particular the “Results” paragraph was focused on the results of primary and secondary objectives.

Methods:

- Longitudinal study, but the current study seems a cross-sectional analysis. That should be more clear in design.

Answer: The Methods paragraph (rows 117-123) was changed and clarifications about study design were provided.

- Many outcomes are included. Why so many?

Answer: We wish to thank the Referee for this comment. Indeed, the collected measures were included in a multidimensional assessment of the patient, becoming part of the exploratory-type investigation on factors associated with pre-determined clinical appearances. Thus, the definition “Outcome measures” seems improvable. Accordingly, we changed it into “Multidimensional assessment” (see row 165).

- Please provide more information about the Night-time, morning and day-time symptoms of COPD questionnaire. This is an important outcomes, but details (eg about scoring) are missing).

Answer: The “Methods” paragraph was completed with some more details about the Night-time, morning and day-time symptoms of COPD questionnaire (see rows 168-177); the original questionnaire was uploaded as Additional file too. Details about scoring calculation were not provided in the paper because, according to authors indications, no score should be calculated and only descriptive analysis (in terms of frequency distribution of items) is allowed.
IN the statistical analyses it is stated "main outcomes" are dyspnea, HR-QoL, etc”. IN my opinion, the main outcome should be circadian symptoms.

Answer: In the “Statistical Analyses” subparagraph the sentence containing “main outcomes” was rephrased (see rows 228-232).

Results:

- Full titles of figures do not need to be reported in the text.

Answer: The text was updated as requested (rows 244, 266-267, 274-275).

- What is considered a satisfactory score? How do you know > 6 is satisfactory?

Answer: We thank the Reviewer for giving us the opportunity to clarify this issue. Indeed, no cut off exists for the level of confidence in attributing the phenotype; we have therefore removed the word "satisfactory" (see row 249). For sake of clarity, in the “Methods” paragraph indication about the meaning of 0 (no confidence at all) and 10 (maximum of confidence) was added (see rows 155-156).

- Figure 2 and 3 is of low quality and difficult to read/not readable.

Answer: We thank the Reviewer for the advice. Figure 2 was changed and, to improve readability, Figure 3 was splitted in 3 distinct figures (a,b,c). The “Results” and “Figures caption” paragraphs were modified accordingly (see row 274 and 695-702).

- Footnotes are missing in the table to explain abbreviations

Answer: The footnotes of the tables were moved underneath the table. Moreover, missing abbreviations of eGFR, FEV1, FVC and mMRC were added in footnotes of Tables 1 and 2.

- It is indicated that proportion of subjects with night time subjects was higher in the CB group compared to other groups. I suggest to perform statistical analysis to test this difference, but write in the limitation that this should be interpreted with caution.

Answer: Following the suggestion of the Reviewer, a Chi-square test to test the association between presence/absence of night-time symptoms and clinical phenotype (CB, EM, MCA) was
performed and p-value resulted in 0.0016, supporting the higher frequency of night-time symptoms in CB patients compared to EM. Even if obtained p-value is higher than significance threshold (set to 0.0005), it should be noted that this threshold was extremely conservative. This is the reason why, we can consider the result of the Chi-square test as suggestive of a real higher frequency of night-time symptoms in CB patients compared to EM.

Result of the Chi-square test has been added in the “Results” paragraph (see rows 267-268) and the Abstract was updated accordingly (see row 52).

The paragraph on line 213-224 is really difficult to read, given all the numbers and different tests.

Answer: We thank the Reviewer for the suggestion. The Table 4 was added and the paragraph (rows 282-293) was updated accordingly.

In the methods it is stated that IPAQ is reported both continuous and categorical, but in table 3 only the categorical results are reported. What about the continuous outcome?

Answer: We confirm that, according to IPAQ scoring algorithm (Ref. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ) – Short and Long Forms November 2005), IPAQ score can be calculated both as continuous and categorical.

For sake of clarity in the previous version of the paper we already showed IPAQ total score in classes (in Table 3).

For homogeneity reasons, in this revised version of the paper, we preferred to show results about the frequency of COPD symptoms vs level of physical activity considering the IPAQ total score in classes and not as continuous (see Table 4).

Moreover, Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ) – Short and Long Forms November 2005 were added in the References paragraph.

Regarding the differences between phenotypes in Qol, sleep, mood and physical activity it would be helpful to have the exact numbers as well, instead of only p-values.

Answer: We thank the Reviewer for the useful suggestion. The Table 4 showing results about the association between circadian rhythm of symptoms and Qol, sleep, mood and physical activity was added and the Results paragraph (rows 295-306) was updated accordingly.
- Why did the authors choose to dichotomize the symptoms? Why not use continuous variables?

Answer: According to authors indications, no score(s) should be calculated for the Night-time, morning and day-time symptoms of COPD questionnaire. In the questionnaire (now attached as Supplementary material), the items F-7, F-18 and F-26 regarding on night-time, early-morning and day-time symptoms, respectively, are collected as presence/absence.

This is the reason why statistical analyses performed to evaluate primary (i.e. frequency of symptoms) and secondary objectives (i.e. association between symptoms and Qol, quality of sleep, level of anxiety/depression) had to consider dichotomized (presence/absence) symptoms.

Discussion:

- Main finding is clearly stated. However, it was not tested whether this differences was statistically significant, nor there is any discussion regarding whether this is clinically relevant.

Answer: We thank the Reviewer for this suggestion. We modified the text accordingly (see rows 358-366).

- See also literature of van Buul et al. about morning symptoms and physical activity over the day in COPD patients


Answer: In the current study, the level of physical activity did not significantly differ in CB and EM patients with (early-morning, day-time or night-time) symptoms respect to those without them. A large body of literature, as properly indicated by the Reviewer, supports the notion that morning symptoms are common in COPD and have a negative influence on a patient’s life. In this respect, patients with high morning symptoms are characterized by a sedentary lifestyle, being associated with low physical activity. We have attempted to address this apparent contradiction in the revised version of the manuscript (see rows 384-392).
- Please do not repeat exact number in discussion

Answer: We have followed the request of the Reviewer and deleted numbers in the Discussion section.

- It is recommended to assess nocturnal symptoms, but what should we do if we are aware of the presence of those symptoms?

Answer: We have addressed the request of the Reviewer by expanding the related paragraph (see rows 378-383).

- First sentence of conclusion is not so clear and not in line with study findings.

Answer: We have simplified the first sentence of the Conclusion section for the sake of clarity.