

## Peer Review File

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### Reviewer A

Comment 1: The authors have attempted to correlate dyspnea and quality of life (QOL) assessment questionnaires with objective assessment of exercise capacity with CPET. The questionnaires chosen for this purpose are appropriate as these are most commonly used in practice.

Reply: We concur that this is an important point. Our intention was to assess dyspnea and quality of life (QOL) using questionnaires that are widely accessible and easily understood. We believed that applying well-established and easily accessible instruments would offer more clinical significance, setting our study apart from previous research.

Comment 2: The authors have found that high mMRC  $>2$  and CAT  $>10$  correlate with poor exercise capacity as evidenced by lower VO<sub>2</sub> max and higher vd/vt peak. This is not a surprising finding, and yet provides more support to making therapy changes based on changes in reported symptoms that are easily assessed by the mMRC and CAT scales.

Reply: We wholeheartedly agree with your observation. Although it may be somewhat expected that patients with a high mMRC grade and CAT score would exhibit poor exercise capacity, lower VO<sub>2</sub> max, and higher VD/VT peak, this finding, as you mentioned, supports the need for treatment modification based on symptom changes. Furthermore, we aimed to provide comprehensive information on interpreting CPET results in patients with COPD. By dividing the results according to symptom severity, we supplied mean values of numerous CPET parameters for each group. As the extent to which CPET parameters change in COPD patients with severe symptoms is not well-established, our findings contribute to a more accurate evaluation of COPD patients using CPET.

Comment 3: The authors recommend that CPET be used to determine exercise capacity and certain VO<sub>2</sub> cutoffs be used to make therapy changes in COPD patients. This may not be practical as CPET is not widely available, difficult to perform in more symptomatic patients, and provides objective assessment of what can be easily discerned from use of simple questionnaires. mMRC  $>2$  & CAT  $>10$  currently qualify as GOLD B and more aggressive treatment is recommended already for GOLD B than GOLD A (mMRC $<2$ , CAT $<10$ ).

Reply: We concur that CPET may not be widely accessible and can be challenging to perform in patients with more severe symptoms. However, unlike other tests, CPET

provides a unique assessment of a patient's maximal exercise capacity, making it highly valuable in determining the underlying cause of exercise intolerance. Dyspnea in COPD patients is often multifactorial due to the prevalence of comorbidities in this population. To enhance the test's relevance for evaluating COPD, we sought to establish a correlation with symptoms, a factor of significant clinical importance in COPD patients.

Comment 4: More importantly, the study reminds us of the importance of symptoms and QOL assessment in COPD patients, in addition to obtaining PFT's. At rest patients with different FEV1 levels may not seem different but exertion will bring about limitations. Symptoms and QOL changes should trigger therapy changes. This becomes particularly important for patients whose COPD is managed by non-pulmonary physicians who may not be used to obtaining mMRC and CAT scores. I recommend that the authors emphasize the importance of symptom and QOL assessment for all COPD patients irrespective of who their disease is being managed by as these correlate with exercise capacity.

Reply: We wholeheartedly agree with this comment. To emphasize the necessity of evaluating symptoms and QOL for all COPD patients, we have incorporated the following paragraph into the revised manuscript.

“In this study, we assessed dyspnea and quality of life in patients with COPD using the mMRC grade and the CAT score, both of which are readily available in clinical settings. The mMRC grade and CAT score demonstrated a significant correlation with VO<sub>2</sub> max and VD/VT peak, substantiating the validity of these two straightforward questionnaires. Therefore, we advocate for the increased utilization of these tools by physicians when assessing patients with COPD.”

(See page 11, lines 208–212 in the Discussion section of the revised manuscript)

Comment 5: In addition to the limitations mentioned by the authors, due to the retrospective nature of the study it is also difficult to tell if any/ how many of the COPD patients that underwent CPET testing, had had any recent COPD exacerbation as this would affect the results of the CPET. I recommend that the authors include this limitation unless they have data on this.

Reply: We appreciate your insightful comment. At our center, we typically do not perform CPET on patients who have experienced COPD exacerbation within the past two months. Furthermore, we reexamined the data for recent exacerbations and confirmed that none of the patients included had experienced any. As a result, we have included the following statement in the exclusion criteria section of the revised manuscript.

“(5) any COPD exacerbation within the previous two months.”

(See page 5, line 81 in the Methods section of the revised manuscript)

Comment 6: The results of this study are not generalizable as: i. majority of the patients are males, ii. was performed in an Asian population.

Reply: We acknowledge the limitations you highlighted and have incorporated the following sentence into the Discussion section of the revised manuscript to address these concerns.

“Moreover, the generalizability of our findings is limited, as the majority of patients were male and the research was conducted exclusively on an Asian population.”  
(See page 11, lines 214–215 in the Discussion section of the revised manuscript)

## **Reviewer B**

In this study, the authors investigated the value of CPET parameters in assessing symptoms and quality of life in Asian patients with COPD. They concluded that maximal oxygen uptake (VO<sub>2</sub> max) and physiological dead space / tidal volume ratio at peak exercise (VD / VT peak) comprehensively reflect symptoms (mMRC) and quality of life(CAT) in patients with COPD. But this study seems like nothing new in their findings.

Comment 1: Please describe how the optimal threshold to predict QOL estimated using mMRC and CAT scores in COPD patients can be applied clinically.

Reply: We appreciate your insightful comment. It is true that patients with COPD often experience extrapulmonary issues, which makes CPET a valuable tool for their evaluation. However, the understanding of how CPET parameters change with disease progression and the extent of clinically significant changes remains limited, unlike other objective measures such as FEV<sub>1</sub> in spirometry. Due to this lack of data, clinicians may hesitate to perform CPET. Our study aimed to determine the degree of change in CPET parameters that would reflect clinically significant changes in subjective symptoms, which are critical for COPD treatment. By understanding these changes, we can provide guidance on the appropriate level of clinical intervention and facilitate broader use of CPET in COPD patient evaluations. We have incorporated these points into the revised manuscript.

“The extent to which CPET parameters vary as a disease progresses, and the clinical significance of such changes, remain inadequately understood compared to other objective measurements like FEV<sub>1</sub> in spirometry. This lack of data contributes to a reluctance to utilize CPET, despite its proven usefulness.”  
(See page 10, lines 184–187 in the Discussion section of the revised manuscript)

“Additionally, improved interpretation of CPET results would facilitate its broader application in clinical practice.”

(See page 10, lines 189–190 in the Discussion section of the revised manuscript)

Comment 2: Although the authors evaluated the correlation between CPET parameters and patients’ symptoms using the mMRC scale and CAT, fewer patients with COPD had severe symptoms (mMRC $\geq$ 2: 12.9%).

Reply: We concur with your observation. As mentioned in the discussion section of our paper, our study included fewer patients with severe symptoms. This is because patients with resting hypoxemia are less likely to undergo CPET, and those who do often perform submaximal exercise for various reasons, such as dyspnea and deconditioning.

Comment 3: You would had better do a multivariate analysis as well as a univariate analysis

Reply: Thank you for thoroughly reviewing our study and providing helpful comments. As you recommended, we conducted a multivariate analysis to assess the association between CPET parameters and severe symptoms (mMRC  $\geq$  2 and CAT  $\geq$  10, respectively). When severe symptoms were defined as mMRC  $\geq$  2, maximal voluntary ventilation (MVV) and VD/VT peak were associated with severe symptoms. However, when severe symptoms were defined as CAT  $\geq$  10, no CPET parameters were associated with severe symptoms. MVV is a well-known indicator of ventilatory capacity, including respiratory muscle strength, and the association between low MVV and more severe dyspnea is understandable. We have incorporated the results of the multivariate analysis in the results section and added Supplementary Tables 1 and 2.

“CPET parameters exhibiting differences between the two groups were subjected to logistic regression analysis, and the findings are summarized in Supplementary Tables 1 and 2. Maximal voluntary ventilation (MVV) and VD/VT peak emerged as independent predictors of severe dyspnea.”

(See page 8, lines 140–143 in the Results section of the revised manuscript)

Supplementary Table 1. Multivariate odds ratios (ORs) from logistic regression with severe dyspnea (mMRC  $\geq$  2)

<b>CPET parameters</b>	<b>Adjusted OR (95% CI)</b>	<b>P value</b>
<b>VO<sub>2</sub> max, L/min</b>	0.426 (0.003 –	0.736
<b>WR max, W</b>	0.991 (0.961 –	0.591
<b>HRR, beats/min</b>	1.027 (0.989 –	0.168
<b>O<sub>2</sub> pulse max, mL/beat</b>	1.018 (0.872 –	0.821
<b>V<sub>E</sub> max, L/min</b>	0.970 (0.872 –	0.573
<b>MVV, L/min</b>	0.930 (0.890 –	0.002
<b>Peak P<sub>ETCO2</sub>, mmHg</b>	0.827 (0.684 –	0.05

<b>V<sub>D</sub>/V<sub>T</sub> peak</b>	0.000 (0.000 –	< 0.001
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Supplementary table 2. Multivariate odds ratios (ORs) from logistic regression with poor quality of life (CAT $\geq$ 10)

<b>CPET parameters</b>	<b>Adjusted OR (95% CI)</b>	<b>P value</b>
<b>VO<sub>2</sub> max, L/min</b>	0.232 (0.016 – 3.470)	0.290
<b>WR max, W</b>	0.986 (0.968 – 1.005)	0.151
<b>HRR, beats/min</b>	1.010 (0.990 – 1.030)	0.320
<b>V<sub>E</sub> max, L/min</b>	1.029 (0.971 – 1.090)	0.336
<b>MVV, L/min</b>	0.982 (0.963 – 1.002)	0.071
<b>Peak P<sub>ETCO<sub>2</sub></sub>, mmHg</b>	1.019 (0.920 – 1.128)	0.719
<b>V<sub>D</sub>/V<sub>T</sub> rest</b>	114.720 (0.226 –	0.136
<b>V<sub>D</sub>/V<sub>T</sub> peak</b>	0.012 (0.000 –	0.433

## Reviewer C

Follow my comments:

### METHODS

Comment 1: In the results you presented groups (mMRC grade 2; CAT score 10), however, you didn't mentioned this information in methods. Do it.

Reply: We completely agree with your comment. To address this, we have added the following sentence to the methods section of the revised manuscript.

“Patients were stratified into two groups based on mMRC grade (either < 2 or  $\geq$  2) and CAT score (either < 10 or  $\geq$  10), differentiating those with less subjective and more subjective complaints.”

(See page 6, lines 90–91 in the Methods section of the revised manuscript)

Comment 2: Which statistical test did you use to compare the groups? This information is missing. You need to detail which test was used in each comparison.

Reply: We completely agree with your comment and would like to apologize for the omission of this information. We used the Student's t-test to compare the groups. To clarify this, we have added the following sentence in the revised manuscript.

“The comparison of CPET parameters among groups stratified by symptom severity was conducted using Student's t-test.”

(See page 7, lines 111–112 in the Methods section of the revised manuscript)

Comment 3: You used Pearson's correlation test for continuous variables and

Spearman’s correlation for categorical variables. Well, Pearson’s correlation must be used for data with a gaussian distribution and Spearman’s correlation must be used for data without a gaussian distribution. You need to check your data analyses (did you analyze in this way?) and correct any mistake (it can compromise your results). You must bring this detailed information into the methods.

Reply: We concur that you raised a crucial point. When the number of samples exceeds 30, continuous variables often follow a normal distribution. As such, we initially used Pearson's correlation test to analyze the correlation between CPET parameters and CAT score. However, following your suggestion, we conducted a Kolmogorov-Smirnov test to verify if the data follows a Gaussian distribution and found that the CAT score data does not. Consequently, we employed Spearman's correlation instead of Pearson's correlation to analyze the correlation between CPET parameters and CAT score, updating the related text (methods and results), Table 5, and Figure 3 accordingly. For mMRC grade, a categorical variable ranging from 1 to 4, we used Spearman's correlation since it does not follow a Gaussian distribution.

“For variables that did not follow a normal distribution, Spearman's correlation coefficients were employed.”

(See page 7, lines 113–114 in the Methods section of the revised manuscript)

(Also see revised Table 5 and Figure 3)

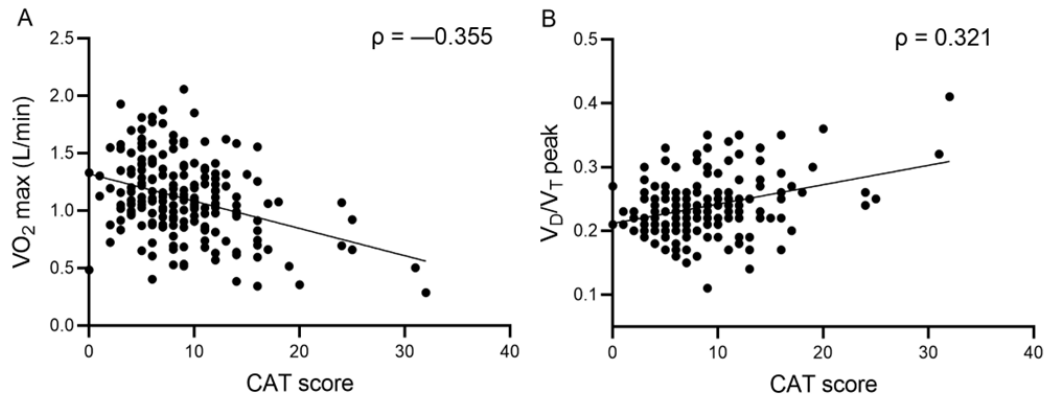
**Table 5.** Correlations among mMRC grade, CAT score, CPET parameters, and FEV<sub>1</sub>

Variables	mMRC grade		CAT score	
	$\rho^\dagger$	<i>P</i> value	$\rho^\dagger$	<i>P</i> value
<b>VO<sub>2</sub> max, L/min</b>	-0.295	< 0.001	-0.297	< 0.001
<b>VO<sub>2</sub> max,</b>	-0.282	< 0.001	-0.252	< 0.001
<b>FEV<sub>1</sub></b>	-0.387	< 0.001	-0.299	< 0.001
<b>O<sub>2</sub> pulse</b>	-0.195	0.006	-0.142	0.047
<b>Anaerobic</b>	-0.135	0.07	-0.194	0.009
<b>Breathing reserve</b>	-0.108	0.13	-0.122	0.089
<b>ETCO<sub>2</sub></b>	-0.131	0.068	-0.145	0.043
<b>V<sub>E</sub> max</b>	-0.248	< 0.001	-0.232	0.001
<b>V<sub>D</sub>/V<sub>T</sub> peak</b>	0.256	< 0.001	0.271	< 0.001

$\dagger$ Spearman’s correlation coefficient.

Abbreviations: VO<sub>2</sub> max, maximal oxygen uptake; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; FEV<sub>1</sub>, forced expiratory volume in 1 s; V<sub>E</sub>, minute ventilation; V<sub>D</sub>, dead space volume; V<sub>T</sub>, tidal volume.

**Figure 3.** Correlation of VO<sub>2</sub> max (L/min) (A) and V<sub>D</sub>/V<sub>T</sub> peak (B) with CAT score.



## RESULTS

Comment 4: Let the baseline characteristics only in the table 1. You don't need to keep in the body of the text. Table 1 is well structured and brings all necessary information.

Reply: We appreciate your helpful comments. We have eliminated the redundant texts that were already included in Table 1.

(See page 7, lines 128–129 in the Results section of the revised manuscript)

Comment 5: The same for table 2. You don't need to bring the values of CPET parameters to the body of the text. Table 2 is well structured and brings all necessary information.

Reply: We are grateful for your helpful comments. We have removed the unnecessary texts that were previously stated in Table 2.

(See page 7, line 129 in the Results section of the revised manuscript)

Comment 6: "The CPET results were compared between less subjective and more subjective complaints, which were divided according to mMRC grade ( $< 2$  or  $\geq 2$ ) and CAT score ( $< 10$  or  $\geq 10$ )". You must to move this stratification methods information to METHODS. Let in the results only how many patients were in each group and the data analyses results.

Reply: Thank you for your thorough review and helpful comments. We have relocated the information regarding the stratification methods to the methods section and revised the results section accordingly.

"The comparison of CPET results between groups with less subjective and more subjective complaints are shown in Tables 3 and 4."

(See page 7, lines 130–131 in the Results section of the revised manuscript)

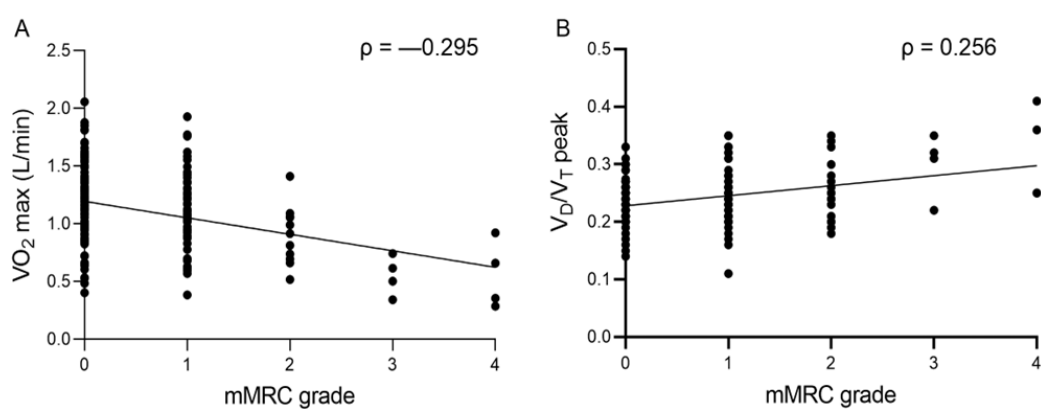
Comment 7: In the text, you mentioned that  $VO_2 \text{ max}$ ,  $VE \text{ max}$  and  $Vd/VT \text{ peak}$  are in figures 3 and 4, however,  $VE \text{ max}$  isn't. Please correct the information.

Reply: Thank you for your detailed comment and our apologies for the inaccurate information. We have removed the part of the sentence that mentioned VE max. (See page 8, lines 144–147 in the Results section of the revised manuscript)

Comment 8: You must to change figure 2 graph type (the presented is a box plot type). Change for the same graph type of figure 3 (including r values).

Reply: We appreciate your thorough review of our study and the helpful comments. Per your recommendation, we have changed the graph type of Figure 2 to a scatter plot.

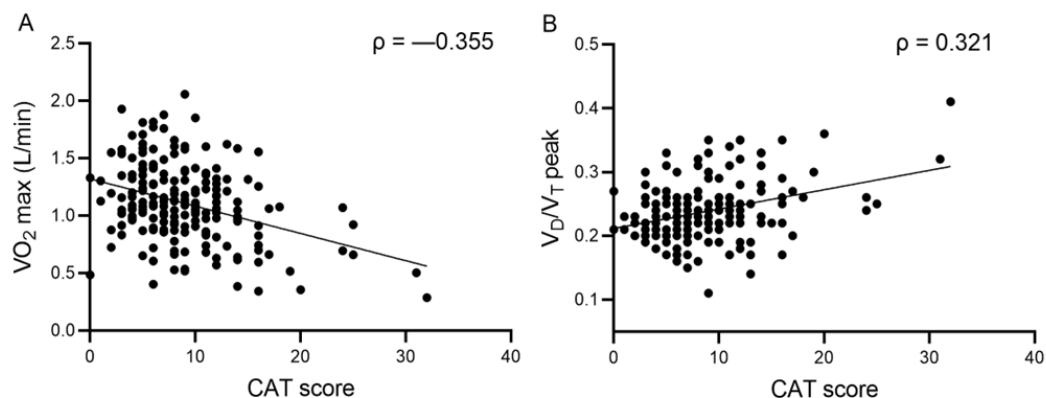
(See revised Figure 2)



Comment 9: In figure 3 you bring different colors (light and dark grey) circles. What does it mean? Any subtype group? Put this information in the legend.

Reply: Thank you for your valuable comment. We apologize for any confusion caused by the different colors. To prevent confusion, we have unified the colors into one.

(See revised Figure 3)





Comment 10: In figure 4, you must remove "For predicting the onset of significant... Vd/Vt peak (D) was 0.235" from the legend. It becomes the legend too long. This information is already in the body of the text. If you want, you can bring this data inside the figure (ex. cut-off = x).

Reply: We concur with your comment. We have removed the part of the figure legend you indicated and added the cut-off value directly within the figure.

*(See revised Figure 4 and Figure 4 legend)*

