

Dear Editor,

We would thank the reviewers for their helpful comments. We answered point-by-point and we hope to have properly addressed all the issues.

Best Regards

#Reviewer1

I have read with great interest the study by Lacotucci et al investigating the characteristics of adult Cystic Fibrosis (CF) patients and the association of frailty with the CF genotyping classification. Overall, the paper is well-written and concise and adds useful information to the everyday clinical practice. The major findings of the study seem to be in accordance with clinical experience. Frailty as the expression of the underlying inflammation has multi-systemic effects. For example, patients often have a decline in the ability to cough and weak cough diminishes the ability of airway clearance. Personally, I find quite interesting the finding that in logistic regression the best predictor of the Pre-Frail/Frail status was the low FEV1 level. This is in agreement with similar findings in patients with other degenerative diseases of the lower respiratory system such as COPD. Indeed, COPD patients with frailty had lower predicted FEV1 values (Wang et al. 2023). Moreover, the frailty phenotype (frail vs robust), but not the frailty index, was associated with lower FEV1.

- Wang L, Zhang X, Liu X. Prevalence and clinical impact of frailty in COPD: a systematic review and meta-analysis. BMC Pulm Med. 2023 May 12;23(1):164. doi: 10.1186/s12890-023-02454-z. PMID: 37173728.

- Hanlon P, Lewsey J, Quint JK, Jani BD, Nicholl BI, McAllister DA, Mair FS. Frailty in COPD: an analysis of prevalence and clinical impact using UK Biobank. BMJ Open Respir Res. 2022 Jul;9(1): e001314. doi: 10.1136/bmjresp-2022-001314. PMID: 35787523.

Reply: We would thank the reviewer for her/his helpful comments. Following the suggestion, we included some sentences reporting these two very interesting articles.
(see Discussion section page 10 from line 298 to line 303)

#Reviewer2

Dear authors, thank you for your article. I have some recommendations, which I hope would improve the article.

Introduction section - you say that 3. *Sweat chloride 48 value 40 to 59 mmol/L with no or 1 CF-causing mutation, but with family history and/or 49 ancillary testing and clinical presentation strongly suggestive of CF* and quote an old guideline from 2008. However, in this guideline it stated that *Individuals with no or 1 CF-causing mutation and clinical findings suggestive of CFTR dysfunction (i.e., obstructive azoospermia, bronchiectasis, or acute, recurrent, or chronic pancreatitis) may be diagnosed with a CFTR-related disorder, depending on their clinical picture or family history, and are at risk for CF*. Please, correct your introduction section, since CF is still considered an autosomal recessive disorder, and two mutations in the CFTR gene are needed. The one mutation you are referring could be defined as CFTR-related disorder.

Reply: We would thank the reviewer for the helpful comments and beg pardon for the introduction of an old reference. Following the suggestion, we changed it introducing the right one with a more extensive description of the diagnostic criteria.
(see Introduction reference 8)
(see Introduction page 2 from line 46 to line 62).

Study population - more information about the types of the disease-causing mutations should be given.

Reply: We agree with the reviewer's comment, and then we introduced some more information about the mutations
(see Table 1)

Results - did some of the included subjects received other therapy, like ivacaftor?

Reply: We introduced this information in the results section
(see Results page 5, from line 180 to line 183)

Discussion - I have no recommendations.

I congratulate you on your nice figures. All the best!

#Reviewer3

Dear authors

I would like to thank you for giving me the opportunity to review the manuscript entitled "Cystic Fibrosis in Adults: A Paradigm of Frailty Syndrome? An Observational Study". The aim of this study was to assess the main clinical and anamnestic characteristics of adult Cystic Fibrosis (CF) patients and to evaluate the association of frailty with the CF genotyping classification. This manuscript is well-designed and -written and provides valuable information that can contribute to future direction to improve the safety and quality of life of people with CF. I have some comments that you can be considered:

- Please apply the full form of abbreviations in the first use

Reply: Beg pardon for this. We introduced all the full forms of the abbreviations in the first use.

- In the introduction, more review of the literature is needed to justify the conduction of this study.

Reply: Following the suggestion, in the introduction, we added some more sentences to explain the need for the study

(see Introduction, page 2 from lines 73 to 83)

- How was the required number of samples determined?

Reply: Because of an observational study, that for the first time assessed the similarity between frailty and the severity of CF, we could not perform a sample size. However, to check the statistical power of the results we used a post-hoc power analysis. The estimated power was calculated considering the FEV1 means in the groups stratified by frailty. We introduced in the Statistical analysis section this information, and in the Supplemental Materials the post-hoc power analysis.

(see Materials and Methods, page 3 line from 1420 to line 145)

(see Supplemental Material Table S1)

- How did you approach the participants and how was the sampling done? It must be fully explained

Reply: Following the reviewer's suggestion, we introduced more sentences on recruitment

(see Materials and Methods page 2 line 93)

(see Materials and Methods page 2 from line 96 to 98)

(see Materials and Methods page 3 from line 101 to 103)

(see Materials and Methods page 3 from line 142 to line 145)

- The way of sampling and completing the questionnaires should be explained in more detail.

Reply: We would thank the reviewer for the helpful comment. To better address this issue, we introduced some sentences

(see Materials and Methods page 3 from line 130 to line 133)

- Please move the table related to logistic multivariate regression analysis to the main text rather than a supplementary file.

Reply: Ok. We introduced the table in the main text.

(see Table 4).