Peer Review File

Comment 1: The abstract is clear and concise and gets the main message of the review article out that QCT is promising but there are some further steps such that it can be used clinically. The article follows the narrative review checklist.
Reply: We appreciate the reviewer's positive feedback on the abstract.
Changes in the text: None.

Comment 2: The introduction is well written and describes the current state of QCT and more broadly COPD.
Reply: We appreciate the reviewer's positive feedback on the introduction.
Changes in the text: None.

Comment 3: The methods are easy to follow and briefly describes paper selection. The bulk of the paper focuses on recent COPD cohort studies, and different ways to quantify emphysema, airway anatomy, air trapping, pulmonary vasculature, ILAs and how these measurements are correlated to pathophysiology of disease. I think these sections nicely summarizes the main take-away features.
Reply: We appreciate the reviewer's positive feedback on these sections.
Changes in the text: None.

Comment 4: The end of the paper describes how QCT can predict COPD exacerbations, extrapulmonary disease and how to use QCT in models to predict key outcomes, such as exacerbations, lung function decline, and mortality.
Reply: We appreciate the reviewer's thorough scrutiny of the content presented in these chapters.
Changes in the text: None.

Comment 5: The conclusion section very briefly touches on some future research priorities. My one suggestion is in this section and to be more specific. The abstract and introduction mentions this paper will go into the clinical applications of QCT and how these different tools as discussed above can be used to affect management decisions and interventions. This should be highlighted-these future research directions/why QCT is not used clinically if there are so many features as discussed above, and what can and should be done moving forward. Maybe focusing on gaps of some different modalities, limitations, rather than just summarizing different studies and cohorts.
Reply: We appreciate the reviewer's feedback regarding future research directions and specific insights. We fully acknowledge the significance of these directions and the substantial impact of QCT on clinical applications and management decisions. In the revised version, we have extensively elaborated on these topics in the conclusion section. We also have provided a

detailed analyze of the challenges that have limited the widespread adoption of QCT in clinical settings.

Changes in the text: Page 11, line 523~536

Revised: However, the use of QCT in clinical settings is currently not widespread, possibly due to technical barriers, high costs, and challenges. The lack of image analysis methods and support for equipment poses a major obstacle, with numerous medical institutions and clinicians struggle to allocate the necessary resources and time to engage in QCT. Additionally, variations in manufacturers and devices can affect the reliability and comparability of QCT results. Despite the significant value of QCT in COPD research, promoting its application requires standardizing the technology, improving cost-effectiveness, and conducting further research and implementation. Future research should focus on developing and standardizing QCT technology, gathering clinical evidence, conducting cost-effectiveness analyses, providing education and training, and offering policy support and insurance coverage. These efforts will advance the use of QCT in COPD management, leading to more accurate and personalized diagnosis and treatment.

Added Reference:

97.Wang JM, Ram S, Labaki WW, Han MK, Galbán CJ. CT-Based Commercial Software Applications: Improving Patient Care Through Accurate COPD Subtyping. Int J Chron Obstruct Pulmon Dis. 2022;17:919-930.

Comment 1: Because tobacco consumption is the main contributing factor in COPD, the prevalence of the disease will increase over the next 20 years in the China, Japan and Asia (THE LANCET 362:1764-1765, 2003). COPD is a significant contributor to global morbidity and mortality. Quantitative computed tomography (QCT), a non-invasive imaging modality, offers the potential to assess lung structure and function in COPD patients.

Reply: We appreciate the reviewer for highlighting the link between smoking and COPD. In the revised version, we have incorporated suitable phrasing to duly acknowledge this significant correlation..

Changes in the text: Page 2, line 62~64

Revised: Smoking is strongly linked to the incidence of COPD, particularly in Asian regions like China where high tobacco consumption contributes to a higher prevalence.

Comment 2: The authors have reviewed published papers using a search in the PubMed database in English from January 1, 2013 to April 20. They summarized that the potential of QCT in providing valuable information on lung volume, airway geometry, airway wall thickness, emphysema, and lung tissue density in COPD patients. Moreover, QCT values have shown robust correlations with pulmonary function tests, and can predict exacerbation risk and mortality in patients with COPD.

They concluded QCT can provide critical insights into the pathogenesis and progression of the disease of COPD. Further research is necessary to determine the clinical significance of QCT measurements for COPD management.

They summarized well the data of DCT data concerning COPD pathogenesis and clinical courses.

Reply: We appreciate the reviewer's recognition of these section.

Changes in the text: None.

Comment 3: However, there are some controversies of diagnostic contribution of QCT on the diagnosis and management of COPD.

In the background of the abstract of the paper, the authors have described that "However, the clinical application of QCT measurements is currently limited, necessitating further evaluation to determine its usefulness in COPD management."

This is not true. The diagnostic value of QCT on COPD have been discussed.

Reply: We appreciate the reviewer for insightful comments regarding limitations of the background section. In light of this valuable feedback, we have made revisions to improve the quality of the paper. . In the revised version, we have incorporated the significance of CT examination in the context of the COVID-19 pandemic. Besides, we have adjusted the wording in specific sections to address conflicting viewpoints.

Changes in the text: Page 1, line 35~39

Revised: Amidst the COVID-19 pandemic, chest CT scans have emerged as a viable alternative for assessing pulmonary function (e.g., spirometry), minimizing the risk of aerosolized virus transmission. However, the clinical application of QCT measurements is not yet widespread enough, necessitating broader validation to determine its usefulness in COPD management.

Comment 4: the most critical point of COPD diagnosis under COVID-19 pandemic is totally neglected. After the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in public, the diagnostic approach for COPD was often disrupted. PFT including spirometry could generate aerosolized droplets, and may increase the risk of transmission of respiratory viruses including SARS-Cov-2 to healthcare workers. Based on this caution of COVID-19 prevention, diagnostic PFT procedures are not recommended under COVID-19 pandemic (Lancet Respir Med. 2020;8:666–667. doi:10.1016/S2213-2600(20)30246-0). On the other hand, COPD is a significant risk for the diseases progression of COVID-19. Thus the alternate modalities for diagnosis of COPD instead of PFT are urgently necessary for the reduction of COPD morbidity and mortality. The QCT may be the strongest modality for the accurate diagnosis of COPD. It seems highly likely that the pandemic will accelerate the type of innovation, the use of new diagnostic tools. While such imaging tools including OCT are increasingly being used in research and clinical settings, they have yet to be consistently adopted for diagnostic work-up for COPD. The type of argument was not discussed in the current review paper.

Teramoto S. The Quantitative Computed Tomography Techniques are Alternate Modalities of Assessing the Disease Profile of COPD Instead of Pulmonary Function Testing Under COVID-19 Pandemic [Letter]. Int J Chron Obstruct Pulmon Dis. 2022;17:2485-2486

https://doi.org/10.2147/COPD.S380026

Reply: We appreciate the reviewer's perceptive observation that our manuscript overlooked the crucial aspect of COPD diagnosis during the COVID-19 pandemic, and we are committed to addressing these concerns thoroughly. In response to this feedback, we have added content

highlighting the importance of using alternative modalities to diagnose and manage COPD while considering the risks associated with traditional pulmonary function testing amidst the pandemic.

Changes in the text: Page 2, line 71~76

Revised: Especially during the COVID-19 pandemic, pulmonary function test procedures should be used with caution, due to the risk of aerosolized virus transmission(4). As a result, innovative diagnostic tools like QCT have gained popularity. QCT can safely evaluate COPD severity, including emphysema and airway obstruction, offering potential as a preliminary screening tool and guide for personalized COPD treatment(5).

Added references:

4.Hull JH, Lloyd JK, Cooper BG. Lung function testing in the COVID-19 endemic. Lancet Respir Med. 2020;8(7):666-667.

5.Teramoto S. The Quantitative Computed Tomography Techniques are Alternate Modalities of Assessing the Disease Profile of COPD Instead of Pulmonary Function Testing Under COVID-19 Pandemic [Letter]. Int J Chron Obstruct Pulmon Dis. 2022;17:2485-2486.