Reply to the comments on manuscript [Lung squamous cell carcinoma presenting as rare clustered cystic lesions: a case report]

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In the second column, unmodified paper content is marked by **BLACK**, modified or added paper content is marked by **RED**, and the statement is marked by **BLUE**.

Reviewer #1	
1. The authors stated that "Blood gas analysis demonstrated severe hypoxemia (partial pressure of oxygen in the arterial blood 60 mmHg, with oxygen 3 L/min via nasal catheter)". However, his PAFI was 187.5, so this patient had moderate hypoxemia.	Thank you for your comment. We have fixed this problem. The modified content is as follows: Arterial blood gas analysis demonstrated type I respiratory failure.
2. Please, the authors could include a full arterial blood gas analysis. This could include pH and CO2. Since the authors stated that the patient had type I respiratory failure.	Thank you very much for your valuable suggestion. We have added pH and CO2. The modified content is as follows: PaO2 60 mmHg, PaCO2 32.1 mmHg, and pH 7.44, with oxygen 3 L/min via a nasal catheter.
Reviewer #2	
1. What is the novelty of the case? - Please make more enrich in the introduction part.	Thank you for your comment. I want to explain to you the novelty of the case. First, Lung cancer associated with cystic airspaces (LCCA) is rare, and squamous cell carcinoma accounts for only 9.1% of LCCA. Through this case, we emphasize that LCCA is prone to misdiagnosis and underdiagnosis. SCC should be considered during the differential diagnosis of solitary cystic lesions. Second, in the present study, there was widely bilateral lung involvement, while no obvious extrathoracic metastasis. The progression and metastasis patterns are very interesting. Based on your valuable advice, we scrutinized our paper and added content to the introduction part. The modified content is as follows: Lung cancer is the leading cause of cancer-related death worldwide[1]. Early diagnosis is critical to improving a patient's chance of

	survival. Low-dose computed tomography (CT) has become an important method for the early screening of lung cancer[2]. On imaging, it typically presents as a mass or nodule. Lung cancer associated with cystic airspaces (LCCA) was first described by Anderson and Pierce in 1954[3]. It is a special form of lung cancer, which is rare in clinical practice, with a reported overall prevalence of 0.46% in a surgical series and 3.7% in a lung cancer–screening cohort[4]. The most common histology was adenocarcinoma, followed by squamous cell carcinoma (9.1%)[5]. Its diagnosis is very challenging and it is increasingly recognized as a cause of delayed diagnosis[6]. We report an unusual case of lung cancer in which the lesion evolved from a solitary thin-walled cyst to bilateral clustered cystic lesions in 4 years (Figure 1A-E). Additionally, there was no obvious extrathoracic metastasis. After chemotherapy, the lesions became clustered thin-walled cysts.
2. Does LCCA often make recurrence? Please discuss that by citing the following article. Lung Adenocarcinoma Presenting as a Soft Tissue Metastasis to the Shoulder: A Case Report. Medicina (Kaunas). 2021;57(2):181. Published 2021 Feb 20. doi:10.3390/medicina57020181.	Thank you very much for your valuable suggestion. We searched the literature and found that there is no definite conclusion. The added content is as follows: Shen et al.[38] evaluated the prognosis by using propensity score matching and found that the LCCA group exhibited a better three-year recurrence-free survival than the non-LCCA group. Shinohara et al.[39] reported that patients with lung cancer adjoining pulmonary bullae (LC-AB) exhibit better overall survival than those with non-LC-AB. M. Kaneda et al.[40]

	stated that LC-AB, even a small lesion, exhibits a poor prognosis. N. Hanaoka et al.[41] reported that postoperative survival of patients with lung carcinoma arising from bullae is comparable to that of patients with lung carcinoma without bullae if the carcinoma is resected in the early stages. In conclusion, the prognosis of LCCA remains controversial because of the rarity of LCCA and inconsistencies in the definitions of LCCA in multiple studies. Thank you for your suggestion on the citation. The added content is as follows: Despite advances in screening, detection, molecular classification, and therapy, a substantial proportion of individuals who initially present with localized or locoregional disease eventually succumb to recurrent malignancy[32]. Local recurrence is seen in 13–24% of patients after curative resection[33, 34] and distant recurrence is reported to be the most common type of the first recurrence[34]. The bone, lung, brain, adrenals, and liver are the most frequent sites of lung cancer metastasis. Occasionally, metastases of lung cancer can be found in the soft tissue, such as the shoulder[35].
3. Is there any methods to detect earlier of the LCCA?	Thank you for the critical comment and helpful suggestion. At present, continuous low-dose CT is the most important method for early diagnosis of LCCA. Liquid biopsy is a promising method for the early diagnosis of lung cancer. Several studies underline the importance of integrating different molecular technologies with imaging, radionics, and artificial intelligence to improve the sensitivity and specificity of early diagnosis. The modified content is as follows: Early identification of any focal lesion is crucial because cancer is typically curable when it is in the early stage[18]. Tumor biopsy is the gold standard for lung cancer diagnosis, but the early lesions with few solid components, LCCA lesions are prone to pneumothorax and other

	biopsy-related complications, which limit the application of biopsy. Based on the results of The National Lung Cancer Screening Trial, low-dose CT screening of heavy smokers has been recommended by the major American and European scientific societies[19-22]. Furthermore, the unpredictable growth rate of lung cancer, which ranges from indolent to aggressive cancers, necessitates attention to the wide spectrum of progression in lung cancer appearance on serial CT scans[23]. The role of 18F-FDG-PET to differentiate between benign and malignant cystic airspace lesions is very limited, since infectious (including fungal) diseases, inflammatory abnormalities, and granulomatous diseases can also show high uptake[24, 25]. Several studies have suggested that cystic airspaces indicative of lung cancer usually develop wall thickening and/or mural nodularity during follow-up[11, 12, 17]. LCCA is usually slow growing[26]. Nevertheless, with tumor growth, airspace size can increase, decrease, or remain unchanged[12, 17]. The drawback of LDCT screening is the presence of uncertainties about high costs, risk of radiation exposure, and false positives observed in the screening population[27]. And late stage cancers still emerge between screening intervals[28]. Liquid biopsy has emerged as a promising tool for the early diagnosis and management of lung cancer due to its non-invasive sampling, easily repeatable, and economic[29]. Liquid biopsy biomarkers include

	cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), microRNA(miRNA), exosomes, and circulating tumor cells (CTCs). The key issue is the sensitivity and specificity of detection for application to early diagnosis. Several studies underline the importance of integrating different molecular technologies with imaging, radionics, and artificial intelligence to improve the sensitivity and specificity of early diagnosis[30, 31].