

Peer Review File

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Reviewer A

This paper presents the findings of CT and PET/CT images of patients with Pulmonary epithelioid hemangioendothelioma (PEH) at the Guangzhou Institute of Respiratory Health by two experienced radiologists, automatic classification through deep learning with these images together with images associated with other pulmonary diseases as controls, and findings in literature in PubMed related to PEH. It is good to try to figure out the features in medical images related to PEH and classify the images through artificial intelligence (AI), which will be helpful in diagnosing the disease in time.

However, more information is required in the manuscript to make the contribution of the paper more clear, the method more informative, and the results more fruitful.

For overall recommendation, the manuscript will be suited to be published after minor revisions.

Reply: We thank the reviewers for their encouragement and comments. These comments have been carefully taken into account and a new revised submission has been uploaded. Please kindly find our reply to the comments below.

My detailed questions/comments/suggestions on the content:

Comment 1: Introduction: what is the diagnosis method for PEH now? The brief description of current PEH diagnosis methods and their advantages/disadvantages will help the audience know the benefits of image findings and classification with the deep learning method.

Reply1:

We appreciate your valuable comment. As the reviewer mentioned, it is important to provide a brief description of current PEH diagnosis and their advantages and disadvantages. This may contribute to a deeper understanding of diagnosis of PEH. Based on your suggestion, a detailed description of PEH diagnosis and their features was added in the undated manuscript. The revised content is as follows.

Changes in the text:

Introduction:

The diagnosis of PEH is based on the histopathological diagnosis after a lung biopsy and a positive immunohistochemical staining for vascular endothelial markers such as CD31^[1]. Histopathological examination can not only be used to diagnose PEH but also help to determine its adverse effects^[2]. Nevertheless, lung biopsy may increase the risk of tumor-related bleeding in patients with PEH, especially for peripheral

lesions^[1]. (See Page 4, Line 69-73)

1. Mesquita RD, Sousa M, Trinidad C, Pinto E, Badiola IA. New Insights about Pulmonary Epithelioid Hemangioendothelioma: Review of the Literature and Two Case Reports. *Case Rep Radiol.* 2017;2017:5972940.

2. Kitaichi M, Nagai S, Nishimura K, et al. Pulmonary epithelioid haemangioendothelioma in 21 patients, including three with partial spontaneous regression. *Eur Respir J.* 1998;12(1):89-96.

Comment 2: Introduction: what are existing studies of image findings? What are the limitations of current image findings (for example, the 54 case reports you reviewed)? Do you get more important findings in your study? Answering these questions in the introduction will let the audience know why you asked two radiologists to analyze the images.

Reply 2:

Thanks for the the reviewer's valuable comments. We agree that it is necessary to explain the existing evidence of image features/limitations of PEH and our findings in current study. In fact, the important findings of this study have been summarized and described in the Discussion section(See Page 9, Line 226-230). Based on your suggestion, we have added more details on the imaging characteristics of PEH in previous studies in Introduction(See Page 4, Line 65-67). The revised content is as follows.

Changes in the text:

Introduction:

The most common manifestation of PEH is bilateral multiple nodules^[1], which may appear in many lung diseases and may be easily misdiagnosed as metastatic cancer ^[2]. (See Page 4, Line 65-67)

The objective of this study is to describe the imaging features of PEH in depth via a retrospective cohort and published cases. On this basis, we further explore the imaging findings that have not clearly been defined and analyze the correlation between imaging features and prognosis. (See Page 4, Line 84-86)

1. Kitaichi M, Nagai S, Nishimura K, et al. Pulmonary epithelioid haemangioendothelioma in 21 patients, including three with partial spontaneous regression. *Eur Respir J.* 1998;12(1):89-96.

2. Mesquita RD, Sousa M, Trinidad C, Pinto E, Badiola IA. New Insights about Pulmonary Epithelioid Hemangioendothelioma: Review of the Literature and Two Case Reports. *Case Rep Radiol.* 2017;2017:5972940.

Comment 3: Method: For the review of published cases, did you ask your radiologists to analyze the images published to get new findings or did you summarize the existing findings in the literature? Which way you used for the 54 case reports should be stated.

Reply 3:

We thank the reviewer's careful review. Our review of a total of 54 case reports encompassed 71 patients with PEH. For cases with CT images, their imaging features were summarized based on the evaluation by our radiologists and the results reported in the literature. If the CT images are not available in cases, summary analysis are mainly conducted according to the description of imaging features provided in the literature. Based on your comment, we have added this information to the Method of the latest manuscript.

Changes in the text:

Method:

For cases with CT images, their imaging features were summarized based on the evaluation by our radiologists and the results reported in the literature. If not, summary analysis is mainly conducted according to the description of imaging features provided in the literature. (See Page 6, Line 145-147)

Comment 4: Method: More detailed deep learning method description is expected in the text. For example, what platform did you use for CNN, is it TensorFlow or something else?

Reply 4:

We appreciate your valuable comment. As the reviewer mentioned, a clear description of deep learning method is important. Based on your suggestion, we have added more details on the statistical analysis of deep learning method in the revised manuscript. The revised content is as follows.

Changes in the text:

Method:

The ResNet is implemented with pytorch, and the model is optimized with SGD algorithm. The batch size of the training data is 5. The learning rate is 1e-4. (See Page 6, Line 132-133)

Comment 5: Results and discussion: What are the differences between your image findings and reported image findings? Is it possible to verify your image findings?

Reply 5:

We appreciate and agree with your point that it is necessary to discuss the differences between our imaging findings and previous studies. In fact, the relevant content have been described in the discussion section. Based on your suggestion, we provide a

detailed summary of the differences of imaging findings from previous studies as follow.

First of all, we summarized the PEH cases in our center and published in the past to better describe the imaging features of PEH as comprehensively as possible(See **Page 9, Line 209-222**). Secondly, we also found imaging manifestations manifested as solitary pulmonary nodules, endobronchial lesions and atelectasis according to the consensus of EHE. These have been described in a few case reports^[1-3](See **Page 10, Line 257-259**). Meanwhile, it was found that PEH patients with pleural effusion may be associated with a poorer prognosis in summarizing data from previous literature, which is also consistent with the results of previous retrospective studies^[4](See **Page 11, Line 273-274**).

1. Fagen K, Silverman ED, Cole RL. Detection of a pulmonary epithelioid hemangioendothelioma by FDG PET scan. Clin Nucl Med. 2004;29(11):758-759.
2. Sakata KK, Gotway MB, Smith ML, et al. Pulmonary Epithelioid Hemangioendothelioma Diagnosed With Endobronchial Biopsies: A Case Report and Literature Review. J Bronchology Interv Pulmonol. 2016;23(2):168-173.
3. Mesquita RD, Sousa M, Trinidad C, Pinto E, Badiola IA. New Insights about Pulmonary Epithelioid Hemangioendothelioma: Review of the Literature and Two Case Reports. Case Rep Radiol. 2017;2017:5972940.
4. Bagan P, Hassan M, Le Pimpec Barthes F, et al. Prognostic factors and surgical indications of pulmonary epithelioid hemangioendothelioma: a review of the literature. Ann Thorac Surg. 2006;82(6):2010-2013.

Comment 6: Results and discussion: Besides the accuracy results, the confusion matrix of the deep learning results should be shown, where you can calculate all metrics, like accuracy, precision, recall, F1 score, etc. More discussions based on these metrics are expected.

Reply 6:

Thank you for pointing this out. Based on your comment, we have further calculated some metrics to show the results of our deep learning model and discuss their meaning in our manuscript. The revised content is as follows.

Changes in the text:

Method:

Model discrimination was assessed using machine learning evaluation metrics, including accuracy, precision, recall, and F1 score. (See **Page 6, Line 134-135**)

Result:

The models discrimination performance including accuracy, precision, recall, F1 score were also been evaluated. The accuracy is 73.4%, the precision is 18.7%, the recall is 18.4%, and the F1 score is 18.5%, respectively. (See **Page 8, Line 205-208**)

Discussion:

It is well known that commonly used metrics for evaluating machine learning algorithms are accuracy, precision, and recall^[1]. In large-sample machine learning in general recall and precision show a significant negative correlation^[2]. (See Page 11-12, Line 296-299)

In our study, probably due to the insufficient sample size, our metrics such as precision, recall, and F1 score are lower compared to other studies ^[3-4]. (See Page 12, Line 300-302)

1. Park SY, Kim YW, Song YR, et al. Compound-level identification of sasang constitution type-specific personalized herbal medicine using data science approach. *Heliyon*. 2023;9(2):e13692.
2. Liang Y, Wang H, Yang J, et al. A Deep Learning Framework to Predict Tumor Tissue-of-Origin Based on Copy Number Alteration. *Front Bioeng Biotechnol*. 2020;8:701.
3. Tian G, Wang Z, Wang C, et al. A deep ensemble learning-based automated detection of COVID-19 using lung CT images and Vision Transformer and ConvNeXt. *Front Microbiol*. 2022;13:1024104.
4. Wang SH, Nayak DR, Guttery DS, Zhang X, Zhang YD. COVID-19 classification by CCSHNet with deep fusion using transfer learning and discriminant correlation analysis. *Inf Fusion*. 2021;68:131-148.

Reviewer B

Comment 1: Pathological findings are important for the diagnosis of pulmonary epithelioid hemangioendothelioma. In recent years, there have been an increasing number of reports of diagnosis based on bronchoscopic biopsy specimens as well as resection specimens, and although TableA3 suggests that 22 cases were diagnosed based on surgical specimens, it would be better to describe what specimens were used for the diagnosis in the 25 cases.

Reply 1:

We thank the reviewer for the valuable comments. Of the 25 patients in our center, 14 patients(56%) underwent surgical lung biopsy, 7(28%) underwent percutaneous lung biopsy and 4(16%) underwent transbronchial lung biopsy. (See Page 8, Line 161-163). Based on your suggestion, we have added this information to the Method of the latest manuscript.

Changes in the text:**Method:**

Each patient was examined by histopathology and diagnosed according to the EHE consensus^[1]. (See Page 5, Line 93-94)

Result:

14 patients(56%) underwent surgical lung biopsy, 7(28%) underwent percutaneous

lung biopsy and 4(16%) underwent transbronchial lung biopsy. (See **Page 7, Line 160-162**)

1. Stacchiotti S, Miah AB, Frezza AM, et al. Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts. *ESMO Open*. 2021;6(3):100170.