

Dear Editor in chief,

Thank you for your timely feedback and the comments from the reviewers. According to your requirements the point- by-point responses to reviewers' suggestions and comments are enclosed.

We believe the manuscript has been highly profited by addressing your suggestions and the reviewers' comments, and it is now much more interesting for readers.

We are very pleased you consider the present manuscript suitable for publication in *World Journal of Radiology*.

Looking forward to hearing from you;
Sincerely,

Prof. Xiao-Dong Yuan, MD, PhD

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The authors describe a novel ct-radiologic technique to examine pulmonary ground glass nodules (GGN) and to asses different ways of blood supply. For this, they examined prospectively 47 patients with GGN in CT and following histopathological diagnosis. The GGN-samples include bronchoalveolarcell carcinoma (BAC) or adenocarcinoma with predominant BAC, atypical hyperplasia, or organizing pneumonia. GGNs were also divided in those with

part solid component and pure GGN. The authors mention the CONSORT statement. The aim of the study is well worth examining, the radiological techniques is sophisticated. But there is a problem with the methodology: GGN-Samples: The details of the patients GGN are not given. Included were GGN of >5mm but the range of GGN and the extent of part solid components is not mentioned, so variability is unclear. What level of solid component led to an exclusion from the study? Sample Size: The 47 GGNs are divided in different histological entities and then subdivided in pure GGN and part solid GGN, reducing the groups sample sizes significantly. One Way ANOVA is used, which is o.k. for smaller groups, but also Pearsons correlation test, with the intent to reveal perfusion-differences in the groups. The overall number of 47 patients and the subgroup sizes are rather small to assess distribution of attributes and allow for such an analysis. Interobserver variation: The study protocol included measures to assess interobserver differences of different radiologists and it gives the definitions used to separate pure GGN from part solid GGN. But there is no data about the extent of interobserver variation. Since the novel radiologic technique used is not widely implemented, the question of interobserver variability would merit a publication itself. The missing informations concerning this aspect do not strengthen the conclusions. Consort Statement. The CONSORT statement is recommended for planning, performing and reporting randomised trials or interventional studies, which does not apply in this case. The STROBE-Protocol might have been more appropriate, but should have been applied before the study was conducted. In the CONSORT- statement provided all items are labeled as irrelevant. This could be a sign of a false study protocol, but more probable it is a sign of underappreciation of these study protocols, which in this case resulted in a flawed methodology. Radiological Technique: The technique is described but it is not mentioned, why the technical protocol was chosen. What were the reasons to do it this way (for example "established standard protocol" or "better definition of GGN" etc.)? What are limitations? If the "study question" was more precise, the methodological problems could easily be avoided. For a question like: "What is the dominant perfusion pattern in pulmonary GGN?" There would be no need to divide the sample

of 47 in subgroups (especially as there seem to be no significant difference between GGN-carcinoma, GGN-hyperplasia and GGN-pneumonia, which could be a minor “sub-question”). Then all pure GGN could be examined against all part solid GGN, regardless of histological type (a division which would have to be clearly defined). The measurements and considerations would be the same, but a more precise question would end in a clearer study design and results of stronger significance. What is more, the Discussion describes why the answer to this question could be of direct clinical significance. This clinical relevance is a strong argument and should not pop up in the Discussion but should be pulled forward to the Introductions of the abstract and the text. To summarize, the article would benefit from some more work on the methodology. A major revision, formulating the “study question” more precisely and focused and putting emphasis on the clinical significance, would improve the article greatly.

Point-by-point responses

- 1. “GGN-Samples: The details of the patients GGN are not given,,,,,, and the extent of part solid components is not mentioned “*

Response: The details of GGNs (Mean \pm SD, range) have been provided in the revised manuscript. Since the borderline of the solid components in mixed GGNs is difficult to define, the extent of part solid components in the GGNs is difficult to determine. We have discussed this as one of the limitations in our study in the “limitation section” of the article.

- 2. “Sample Size: The 47 GGNs are divided in different histological entities and then subdivided in pure GGN and part solid GGN, reducing the groups sample sizes significantly”*

Response: A relatively small sample size is another limitation of our study, which has been discussed in the article “limitation section” too.

Statistically, a relatively small sample size will not affect the reliability of the positive findings of an investigation but the negative ones. So negative findings in our study such as “there is no significant difference of the perfusion parameters between malignant and benign GGNs” may not be reliable and need to be validated by population-based investigation. However other interesting finds, i.e., positive findings in our study are more reliable due to the nature of statistical test.

3. *“The study protocol included measures to assess interobserver differences of different radiologists and it gives the definitions used to separate pure GGN from part solid GGN. But there is no data about the extent of interobserver variation.”*

Response: The inter-observer reproducibility of perfusion parameters (BF, PF and PI) and HU of GGNs has been assessed and provided in the revision.

4. *“The CONSORT statement is recommended for planning, performing and reporting randomised trials or interventional studies, which does not apply in this case. The STROBE-Protocol might have been more appropriate ,,,,,”*

Response: This study was designed and performed according to the STROBE-Protocol. The relevant document is uploaded along with the revised manuscript.

5. *“The technique is described but it is not mentioned, why the technical protocol was chosen. What were the reasons to do it this way “*

Response: The CT perfusion technique employed in this study was developed and reported in a previous study, which was cited in our manuscript as reference 15: Yuan X, Zhang J, Ao G, Quan C, Tian Y, Li H. Lung cancer perfusion: can we measure pulmonary and bronchial

circulation simultaneously? Eur Radiol. 2012;22:1665-1671. [PMID: 22415414 DOI:10.1007/s00330-012-2414-5]

6. *"If the "study question" was more precise, the methodological problems could easily be avoided. For a question like: "What is the dominant perfusion pattern in pulmonary GGN?" ,,,,, There would be no need to divide the sample of 47 in subgroups (especially as there seem to be no significant difference between GGN-carcinoma, GGN-hyperplasia and GGN-pneumonia, which could be a minor "sub-question")"*

Response: The aim of this study is to assess the dual vascular supply patterns of GGNs on different histopathology and opacities. In order to achieve this aim, we divide the sample of 47 in subgroups according to histopathological types and lesions' HU respectively. It is through this method that we found there is no significant difference among different histopathological types of GGNs, which can not be known beforehand. We cannot design a prospective study based on known results, though it seems more perfect.

7. *"the Discussion describes why the answer to this question could be of direct clinical significance. This clinical relevance is a strong argument and should not pop up in the Discussion but should be pulled forward to the Introductions of the abstract and the text."*

Response: We also think the "answer to this question" and clinical relevance may be a strong argument. So put it in the discussion section other than the results and conclusion sections. Furthermore, the relevant contents mainly derived from our study findings, so not suitable to be pulled forward to the Introductions of the abstract.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The manuscript is devoted to the assessment of the dual vascular supply patterns of ground-glass nodules with regard to different histopathology and opacities from perfusion CT data. The authors performed a thorough analysis of data for a relatively large number of patients, specifically 47. Up to this day, not many papers have been published, where the dual vascular supply patterns of ground-glass nodules are evaluated with perfusion CT. That is why the paper might be of interest to the readers. The manuscript is a result of well-done methodical research. It is well organized and written in good English. I found only one fault in grammar (see Comment 3). In my view, the manuscript should be accepted for publication in the World Journal of Radiology. My comments are few and all (except Comment 3) are only recommendations. Comments: 1. Throughout the text the authors use the phrases “pulmonary flow (PF)” and bronchial flow (BF),” every time repeating the abbreviations in the brackets. I think it is not necessary. It is quite enough to introduce the abbreviation once and then use it (for example, PF), or alternate the abbreviation and the phrase (for example pulmonary flow). 2. The Conclusion consists of a single sentence. This is not to the common rules. It is necessary to describe first all results the authors obtained, then formulate the final conclusions, and lastly outline the areas of further research. I would recommend the authors to keep to these rules in writing the Conclusion. 3. Fault in grammar: Page 13/20, last line: “forth” should be “fourth”.

Author response:

We thank the reviewer for taking the time to review our manuscript and giving us positive feedback.

1. *Comments: 1. Throughout the text the authors use the phrases “pulmonary flow (PF)” and bronchial flow (BF),” every time repeating the abbreviations in the brackets. I think it is not necessary. It is quite enough to introduce the abbreviation once and then use it (for example, PF), or alternate the abbreviation and the phrase (for example pulmonary flow).*

Response: It has been revised according to your suggestion.

2. *Comments: 2. The Conclusion consists of a single sentence. This is not to the common rules. It is necessary to describe first all results the authors obtained, the formulate the final conclusions, and lastly outline the areas of further research. I would recommend the authors to keep to these rules in writing the Conclusion.*

Response: The conclusion section has been enriched according to your suggestion.

3. *Comments: 3. Fault in gramma: Page 13/20, last line: “forth” should be “fourth”.* **Response:** The fault in gramma has been corrected.

4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

Response: The revised manuscript has been language polished by a native English speaker.

5 ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT,

ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

The basic rules on abbreviations are provided here:

(1) Title: *Abbreviations are not permitted. Please spell out any abbreviation in the title.*

Response: The title was revised as “Evaluation of the dual vascular supply patterns in Ground-Glass nodules with a dynamic volume computed tomography”.

(2) Running title: *Abbreviations are permitted. Also, please shorten the running title to no more than 6 words.*

Response: The Running title of the revised manuscript is “Dual vascular supply in the GGNs”.

(3) Abstract: *Abbreviations must be defined upon first appearance in the Abstract. Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori).*

Author response: This was done.

(4) Key Words: *Abbreviations must be defined upon first appearance in the Key Words.*

Author response: This was done.

(5) Core Tip: *Abbreviations must be defined upon first appearance in the Core Tip. Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori)*

Author response: This was done.

(6) Main Text: Abbreviations must be defined upon first appearance in the Main Text. Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)

Author response: This was done.

(7) Article Highlights: Abbreviations must be defined upon first appearance in the Article Highlights. Example 1: Hepatocellular carcinoma (HCC).

Example 2: *Helicobacter pylori* (*H. pylori*)

Author response: This was done.

(8) Figures: Abbreviations are not allowed in the Figure title. For the Figure Legend text, abbreviations are allowed but must be defined upon first appearance in the text. Example 1: A: Hepatocellular carcinoma (HCC) biopsy sample; B: HCC-adjacent tissue sample. For any abbreviation that appears in the Figure itself but is not included in the Figure Legend textual description, it will be defined (separated by semicolons) at the end of the figure legend. Example 2: BMI: Body mass index; US: Ultrasound.

Author response: This was done.

(9) Tables: Abbreviations are not allowed in the Table title. For the Table itself, please verify all abbreviations used in tables are defined (separated by semicolons) directly underneath the table. Example 1: BMI: Body mass index; US: Ultrasound.

Author response: This was done.

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

This manuscript describe a novel ct-radiologic technique to examine pulmonary ground glass nodules (GGN) and to asses different ways of blood supply. The topic of this paper is interesting, and similar article is not much, it may provided some useful information for readers. However, there are some concerns. study protocols like CONSORT or STROBE are not used to plan studies beforehand, but are somehow adapted to the study design ex post. So this study adherence to CONSORT may not right. The details of the patients GGN are not given. Please highlight the clinical significance of this study. Please add more reference if possible since the asked references of this type of manuscript is 30 at least. The file "Institutional Review Board Approval Form or Document" is not the asked version, so does the file "Clinical Trial Registration Statement".

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade D (Fair)

Author response:

Thanks for the Science editor's comments and suggestions.

- 1. The CONSORT protocol is not suitable for our study. Actually, we designed and performed this study according to the STROBE protocol though it was not reported during the first submitting. This time we submitted the STROBE statement of our study along with the revised manuscript.**
- 2. The details have been provided in the revised manuscript.**
- 3. The clinical significance of our study has been highlighted and enriched.**
- 4. More relevant references have been added into the revised manuscript.**

5. The Institutional Review Board Approval Document has been upload.
The Clinical Trial Registration Statement is not applicable to this investigation since this study is neither a RCT nor an interventional Clinical Trial.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Radiology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before its final acceptance, the author(s) must provide the Chinese version of the ethical approval document. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words). Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e., generated de novo by the author(s) for this paper). If

the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Author response:

Thanks for the comments and suggestions from the Company editor-in-chief.

- 1. Chinese version of the ethical approval document of our study has been submitted.**
- 2. The title has been shortened in the revised manuscript to meet the requirement of the journal.**
- 3. PowerPoint (PPT) of the original figures has been submitted.**
- 4. The standard three-line tables have been used according to your requirements in the revised manuscript.**
- 5. The funding agency copy of the approval document of our study has been submitted.**