**Response to Editors and Reviewers**

We are pleased to resubmit the manuscript “Liver Multiacinar Regenerative Nodules: Imaging Findings and Clinical Implications” after assessing the suggested revisions. We would like to thank the careful attention and consideration given to this manuscript, the positive feedback and the pertinent suggestions for improvement. Responses to the comments (included in italics) are as follows:

**Editor:**

**Comentário 1**

*O resumo e abstract deverão reflectir fielmente a estrutura do artigo,
pelo que deverá ser incluído um parágrafo independente relativo ao
capítulo "Discussão"*

Resposta: O resumo e o abstract foram re-escritos, incluindo o parágrafo referente ao capítulo “Discussão.”

**Comentário 2**
*O resumo e abstract não deverão incluir abreviaturas.*

Resposta: As abreviaturas foram removidas do resumo e do abstract. As únicas que persistem são as abreviaturas IQR (AIQ em português) de uso comum, correspondendo à amplitude interquartílica da mediana.

**Revisor A:**
**Comment 1**

*Review of
“Liver Multiacinar Regenerative Nodules: Imaging Findings and Clinical
Implications”
This is a really nice article that focus on a quite rare diagnosis and
unwell described in the Literature.
The main focus is trying to define and characterize, in a systematized and
extensive manner, the liver multiacinar regenerative nodules in terms of
clinics, radiology and histology, with a clear focus on MR imaging findings.
This authors’ contribution adds value to what is already published, and is
both relevant and original.*

Response: The authors wish to thank the reviewer’s remarks.

**Comment 2**

*Title: it is instructive and short but I think it could also mention the
type of study (and maybe even to highlight that it was performed in two
Centers) at the end of the sentence to be more informative.*

Response: We have equated the hypothesis to change the title as suggested but it is our opinion that the current formulation conveys the relevant information to the readers without (at this level) a too long potentially less focused title.

**Comment 3**

*Abstract: it is well structured and reflects the content of the manuscript.
Nevertheless, in the Portuguese version I suggest some minor review, mainly:
in the introduction to replace “MRN” for “NRM”; “num diferente
contexto de alterações vasculares hepáticas“ for “num contexto
diferente, de alterações vasculares hepaticas”; delete “portanto”
and replace “hepatopatia crónica” for “doença hepática crónica”.*

 Response: The corrections have been in the revision of the abstract. The change of “NRM for MRN” was not performed since all abbreviations were removed from the abstract as instructed by the editor.

**Comment 4**
*Introduction: The objectives are clearly described and it explains the
relevance of the study.
As liver multiacinar regenerative nodules are not consistently described in
the Literature and are even referred with different designations (as the
Authors also highlight) I think that:
The following 2 sentences should have a reference
number: “They are further subdivided into monoacinar or multiacinar
nodules, cirrhotic regenerative nodules and focal nodular hyperplasia
(FNH)” and “Multiacinar regenerative nodules (MRN) are frequently
grouped together with nodular regenerative hyperplasia, although the latter
is an example of the monoacinar type, with minute micronodular
transformation of a whole or part of the liver.”*

Response: References have been specified for the sentences individually.

**Comment 5**

*It should be mentioned the other names how these lesions
are called besides “FNH-like”, as for example “Large regenerative
nodules” (as stated, for example, in references 1 and 4).*

Response: The designation “Large regenerative nodules” has been added to the Introduction.

**Comment 6**
*I suggest the following grammatical revision (in italic):*

*“An increased incidence in long time cancer survivors previously treated
by chemo or radiotherapy, especially paediatric patients, has also been
described, and the mechanism seems to be related to the non-selective effect
of chemotherapy regimens in the non-tumorous liver.”
The present study aimed to focus at the description of the key imaging
features of MRN in particular those that may preclude a wrong diagnosis of
simple FNH.*

Response: The grammatical corrections have been made.

**Comment 7**

*In the last paragraph it is affirmed that the clinical context of MRN and
FNH are different and that the former one should prompt an investigation of
a possible underlying liver disease and the later not. In regard to this I
think it is important to acknowledge that if FNH are multiple (which can
happen in 20-30% of cases) other diseases should be considered – this is
what is written in the most recent guidelines of EASL on this subject
(“EASL Clinical Practice Guidelines on the management of benign liver
tumours”, 2016), and this reference should also be added as they consist
the main guide in clinical practice in respect to benign liver tumors. The
authors could even discuss hypothetically if this recommendation is made on
a perhaps “wrong” diagnosis of FNH, but maybe this goes beyond the focus
of the article.*

Response: The reference has been added to the Introduction section (reference 18, the remaining references were renumbered). Comments on the “wrong” diagnosis of FNH have been extended in the Discussion and Conclusions sections.

**Comment 8**

*Material and methods: it describes how the objectives were reached and the
study design and methodology seem appropriate to it as the main issue was to
try to differentiate MRN from FNH as they are often called FNH-like lesions
so the “control” group was this one.  The statistical method is
accurate, although with such a small number of patients in each group it may
be difficult to interpret some of them.*

Response: The small number of cases has been added to the limitations mentioned in the Discussion section.

**Comment 9**

*In the section “Patient selection and standard of reference” instead of
“An FNH..” it should be “A FNH..”) in 2 sentences: “Imaging
criteria for the diagnosis of MRN consisted in the demonstration of an
FNH-like nodule on MR imaging, showing temporal stability (minimum follow-up
time of 2 years) and exclusively detected in the clinical context of a known
underlying liver disease.“ and “An FNH diagnosis was made in all cases
where the typical FNH MR imaging criteria were found in an otherwise healthy
patient.”*

Response: The aforementioned grammatical errors have been corrected.

**Comment 10**
*In the section “Image analysis” the word “sub-speciality” lacks an i.*
Response: The correction has been made.

**Comment 11**

*Results: Data presentation and analysis seem accurate and the results clear
and convincing.*

Response: NA

**Comment 12**

*The Authors decided to review just one image in each patient (and they even
refer in the Discussion that it is a limitation of the study) but I think it
would be interesting to know, if the data is available, what was the mean
number of lesions in each patients in both groups and to address if it could
be a discriminant feature.*

Response: The number of lesions was not accounted for in all cases, since it was not a primary focus of the study. They were specifically not reflected in the blinded image review. Granted that it is an important distinguishing factor, as is the clinical context, it was not considered for this study that focuses in individual distinctive imaging characteristics that could be helpful in the differentiation between MRN and FNH, especially when these aforementioned crucial factors are absent or unknown.

**Comment 13***I suggest some minor grammatical revision:
 “IQR”, although it’s obvious, is not written in
full length.
Adding what is in italic: “The mean size of FNH
lesions was 6.20 cm (SD: 3.14) while the mean size of MRN was 2.79cm (SD:
1.36), which was significantly smaller (t=5.056, p<0.001).”*

Response: Interquartile range in full length was added in the Statistical Analysis part of the Methods section. The other correction was also performed.

**Comment 14**
*Discussion: It explains the relevance of the results and describes the
potential limitations. Nevertheless I think another possible limitation to
the study would be the relative small number of patients in each group to
make a proper statistical analysis which can search for statistically
significant differences. Maybe some differences could have reached
statistically significant difference if the number of patients was bigger.*

*It is also well organized and centers in the imaging findings, which is the
main objective of the study.*

Response: The small sample size has been added to the limitations part of the Discussion section.

**Comment 15**

*I suggest to address also 2 other aspects in this section: to state if there
are similar studies with this methodology and objectives or if this is an
“unique” study; and if the Authors think whether there are or not areas
in need of further study.*

Response: These two aspects have been added to the final part of the Discussion section.

**Comment 16**

*Regarding grammatical revision I only suggest minor revision in the
following sentence (in italic):*

*“Also, when dealing with other clinical contexts such
as cirrhosis or chemotherapy-treated patients, the differentiation from
malignancy assumes special importance if one considers that it may appear as
a “de novo” focal liver lesion on follow-up imaging studies”*

Response: The revision has been performed.

**Comment 17**
*Conclusion: I think the conclusions could be more in accordance to the main
objective, which was the imaging differences between MRN and FNH lesions,
although it is also important to maintain what is already written.*

Response: The Conclusion section has been rewritten to accommodate the suggestions from the revisors.

**Comment 18**

*References: The literature review seems adequate. I only suggested adding a
reference in the introduction (see above). And I don’t think it is
necessary, according to AMP author’s guidelines, to include the doi
number.*

Response: The reference has been added and the doi have been removed.

**Comment 19**

*Tables/Figures: The message is clear enough and they are identified and
legible except only for 1 image (10259-31811-1-SP.tiff) which is not clearly
seen.*

Response: Image 10259-31811-1, figure 1D, displays the ADC map corresponding to the b700 diffusion image (10259-31810-1, figure 1C), showing no apparent restriction. The image previously had an arrow pointing to the lesion but was removed due to the initial instructions by the editorial office.

**Revisor C:**
**Comentário 1**

*Deverá ser efectuada uma revisão da linguagem pois existem alguns erros,
como por exemplo manter a abreviatura em inglês (MRN) quando se está a
falar de nódulos regenerativos multiacinares em português, que deverá ser
abreviado por NRM. Tal foi feito correctamente em relação à hiperplasia
nodular focal (HNF vs FNH).*

Resposta: As abreviaturas foram removidas do resumo, de acordo com instruções do Editor.

**Comentário 2**
*Tal como se verifica no presente estudo a esmagadora maioria dos casos de
NRM resulta de uma alteração vascular. No entanto, na literatura (vide
referência 5) são apresentadas ainda como outras causas a necrose e outras
causas. Tal poderá ser referido no texto.*

Respota: A referência a outras causas, tal como mencionado na referência 5, foi incluída na Introdução.

**Comentário 3**

*Os autores poderão querer analisar ainda o artigo:
J Hepatobiliary Pancreat Sci. 2011 May;18(3):386-96. doi:
10.1007/s00534-010-0342-9.
A pictorial review of benign hepatocellular nodular lesions: comprehensive
radiological assessment incorporating the concept of anomalous portal tract
syndrome.
Ueda T1, Starkey J, Mori K, Fukunaga K, Shimofusa R, Motoori K, Minami
M, Kondo F.*

Resposta: A referência foi acrescentada à Introdução, com o número 16. As restantes referências foram consequentemente renumeradas.

**Comentário 4**

*A conclusão em inglês deverá ser reformulada pois está um pouco confusa.
A conclusão em português é mais clara na importância do presente estudo.*

Resposta: As conclusões foram re-escritas, acomodando as recomendações dos revisores.

**Revisor D:**
**Comment 1**

*This is a well-structured and well-balanced manuscript about imaging
differentiation between two benign liver nodules, with relevant clinical
implications.
The self-recognized main limitation of the study is the imperfect standard
of reference, as half of MRN diagnoses were established by imaging only. For
this reason, it would be important to make clear which were the “typical
MR criteria” for the diagnosis of FNH (and FNH-like lesions) the authors
used (as references in this sentence are old or unsuitable).*

Response: The more detailed MR criteria for the diagnosis of FNH and FNH-like lesions were added to the Methods section.

**Comment 2**

*In addition, it is important to know which were the authors’ criteria to
select the “dominant lesion” in case of multiplicity.*

Response: The dominant lesion was the largest lesion that could be depicted alone in an image. This additional information was added to the Methods section.

**Comment 3**

*In “Results”, it is important to make clear if the absence of
macroscopic or microscopic fat components was established by imaging or
pathological criteria.*

Response: The presence of macroscopic or microscopic fat was established predominantly by imaging and this more detailed information was added.

**Comment 4**
*Finally, in “Conclusion” it should be emphasized the results of the
present study, namely the major clues to propose a final diagnosis of MRN:
hypointense rim in contrast-enhanced MR, and lack of a central scar. It is
confusing the reference to multiplicity as a clue to the diagnosis in
“Conclusion”, as this feature is not addressed in the present study.*

Response: The Conclusion section has been rewritten to accommodate the revisors recommendations.

**Revisor E:**
**Comment 1**

*The purpose of the manuscript is to compare of the type of lesions, MRN and
FNH, according some characteristics of the lesions evaluated by the images
collected by MR. The results presented are in line with the objective,
allowing to obtain valid final conclusions.
Although in terms of statistical analysis the paper used only bivariate
analysis, I consider that this could be considered as a first step for a
global understanding of main differences between the two types of lesions
evaluated. However, a mutivariable analysis could be included in order to
improve the results obtained.*

Response: Multivariable analysis was not performed due to the reduced number of cases in each group, similarly to other studies cited in this work, for instance reference 9. This limitation has been added to the Discussion section. A recommendation for larger studies to further explore the imaging differences has also been made, which would include multivariable analysis of the several imaging features.

**Comment 2**

*In the Abstract:
• Some changes may be considered, namely in the results (please consider
the comments below that can be also considered for the abstract).
In the section “Statistical Analysis”:
• Consider mean and standard deviation for the variable “dimension”*

Response: The variable “dimension” has been presented with median and interquartile range, due to the results of the Shapiro-Wilk normality test mentioned in Comment 5.

**Comment 3**

*• The description of the methods used need to be changed. The phrase
“Comparison between continuous variables was conducted using independent
samples t test and between categorical variables using Fisher’s exact
test” is not clear. I.e., in the analysis performed, groups are compared
according continuous or categorical variables.*

Response: The recommended corrections have been made.

**Comment 4**

*• If the crosstab was higher than 2x2, Fisher test was also used? Please
clarify this option.*

Response: No crosstab higher than 2x2 was used since it did not comply with the requirements for Chi square analysis due to the small number of cases. Variables with 3 values were grouped for comparison purposes.

**Comment 5**
*• Normality diagnose was performed for the continuous variable
“dimension” according groups? If yes, the results are consistent with
the use of parametric test?*

Response: Normality was initially assumed for the continuous variable dimension. Having performed the Shapiro-Wilk normality test, normality could not be assumed and so changes were performed, with dimension now being expressed as median and interquartile range. Consequently the test for comparison was changed to the Mann-Whitney U test, which however did not show modifications to the conclusions, also displaying a strong significant difference between both groups (p<0.001).

**Comment 6***Please clarify the option to group categories in some categorical
variables*

Response: Categorical variables with more than 3 values were grouped for comparison purposes, since the requirements for Chi square analysis of tables higher than 2x2 were not met due to the small number of cases. The description of this was extended in the Methods section, signaling that the grouping was performed in order to explore classically reported differences of MRN lesions.

**Comment 7**

*• Some multivariable analyses were performed? If no, I suggest to include
this analysis to improve the results.*

Response: As mentioned above, multivariable analysis was not performed due to the reduced number of cases in each group, similarly to other studies cited in this work. This limitation has been added to the Discussion section and a recommendation for larger studies to further explore the imaging differences has also been made, which would include multivariable analysis of the several imaging features.

**Comment 8**

*In the section “Results”:
• Please take attention with the description of the results. Fisher test
(or Chi-Square test) allow to conclude about the association between
variables.*

Response: The description of the results has been changed accordingly.

**Comment 9**

 *• Please insert % in Table 1*

Response: Percentages have been inserted in Table 1

**Comment 10***• Please insert standard deviation in Table 2 for the variable
“dimension”*

Response: Interquartile range was inserted in Table 2 for the variable dimension, since it was determined that it did not display a normal distribution.

**Comment 11**
*• In Table 2, comments (uptake/present) could be included in the first
columns. Additionally, I suggest to add a new column with the total, and to
exclude the fraction representation. Statistical tests used could also be
included as note in the table, with appropriate indication.*

Response: Comments uptake/present have been moved to the first column. References to the type of statistical test used have also been added in the footnote. The use of fractions is not ideal but it was the solution the authors settled for in an attempt to simplify the table. This is due to the fact that the total numbers are not only different between the groups but they are also different for some of the assessed imaging features. For example, assessing liver specific contrast uptake in the hepatobiliary phase, only 22 out of the 26 MRN cases underwent this specific MR exam and only 18 out of the 25 cases of FNH performed it. This would imply a column for the total numbers for each group.