

Format for ANSWERING REVIEWERS

August 19, 2016

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 27666-review.doc).

Title: Impact of contrast-enhanced ultrasound in patients with renal function impairment

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Name of Journal: *World Journal of Radiology*

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We thank reviewers 00227564 and 00503175 for their positive comments. The revised manuscript incorporated suggestions of the editor and reviewers, as follows:

1 Text format has been updated according to the editor's specifications. In particular, we added the "Comments" section after the Discussion.

2 Revision has been made according to the suggestions of the reviewers. Revised and added sentences have been highlighted in blue in the revised text.

(1) Reviewers 00736367, 00503175 and 00503241 suggested minor language polishing, whereas reviewer 00227564 suggested major language revision. We then asked an English-mother language colleague having the residency in the Institute of Radiology of Udine to refine the text (she has been included in the acknowledgments at the end of the article). Our colleague was of help in correcting grammar errors and refining the text (e.g., by rephrasing unclear sentences). All changes incorporated in the re-submitted manuscript are colored in red. Of note, changes are limited to grammar and syntax, with no substantial modification of the content compared to the original version of the manuscript. We believe that English language is now suitable for publication.

(2) According to the reviewer 00736367, *"the study was well conducted but the use of CEUS in Nephrology departments is widespread today, also for trauma, tumors and response to treatments. There is a more recent bibliography than the one presented which shows how said"*. We agree with the reviewer concerning the widespread use of CEUS in patients with renal failure. However, as we already emphasized in the Introduction and Discussion, such a use reflects experts' opinion (e.g., EFSUM guidelines) rather than an evidence-based status. Despite several attempts on main medical databases (PubMed, Scopus) with different key words, we were not able to find other studies focused on CEUS in patients with renal failure. We believe that the available bibliography refers to the use of CEUS in patients with preserved renal function, as we emphasized in the Discussion.

(3) Reviewer 00503255.

- *"Methods 1. page 6, line 4: "Table 1" did not show patient characteristics, but ultrasound equipment. 2. page 6, line 9: "Table 2" did not show ultrasound equipment, but characteristics of 50 patients with AKI suspicious vascular cause"*. We corrected tables' numeration in the text as suggested by the reviewer (Tab. 1 for the ultrasound equipment and Tab. 2 illustrating patients with AKI of suspicious vascular origin).

- *What definition did you use for "ARF" and "CRF" in this paper?* ARF is usually the worst grade of AKI staging in KDIGO AKI guideline. CRF is the worst grade of CKD staging in KDIGO CKD guideline. We used KDIGO criteria for both ARF and CRF, as we made explicit by adding the following sentence in the "Patients's population" paragraph of the Materials and Methods: "We assessed RFI according to the

Kidney disease improving global outcomes (KDIGO) criteria for both acute renal failure (ARF)^[17] and chronic renal failure (CRF)^[18]". We also modified the references accordingly.

(4) Reviewer 00503241

- 1 *The authors indicate CEUS as valid option to resonance imaging with gadolinium, citing the risk of nephrogenic systemic fibrosis (NSF) related to gadolinium. A brief caution to this point has to be addressed pointing out that NSF was diagnosed only in patients with severe chronic kidney disease stage (stage 5), with the use of old contrast medium used at high dosages. To date there are reported no cases of NSF in patients with normal kidney function. We believe the reviewer focuses on an important topic. There is increasing evidence for a safe profile of macrocyclic gadolinium chelates in patients with renal failure. On the other hand, though one might assume the risk for NSF has been overemphasized, there are still concerns in performing contrast-enhanced MRI in patients with renal failure in clinical practice. This is exemplified by the debate on why NSF should be still considered a relevant issue (e.g., Thomsen HS, J Magn Reson Imaging. 2014;40:11-12), given uncertainty on pathogenic mechanisms and other safety issues (e.g., evidence of gadolinium accumulation in the brain, bone and kidneys) (Rogosnitzky M et al., Biometals 2016;29:365-376). We then modified the Introduction by adding the following sentence: "Although risk for nephrogenic systemic fibrosis (NSF) has been better defined over the last years, concerns still exist for the use of gadolinium chelates in patients with RFI, given uncertainty in pathogenic mechanisms and/or potential additional side effects related to gadolinium accumulation in the brain^[1-4]".*

- 2 *The authors report that using Color Doppler, perfusion abnormalities are often difficult to detect in patients with globally hypoperfused kidneys, and a non-reliable characterization of renal masses is obtained, except for simple cysts: I agree but is CEUS really superior in hypoperfused kidneys? In literature It was not clearly demonstrated, to my knowledge. For the renal masses scenario, the superiority of CEUS over Color Doppler has been recently demonstrated by Bertolotto M et al., AJR 2015;204:W557-W565. We believe that both clinical practice and the results of our study (detection rates for renal infarction of 36% vs 2% for CEUS and US with Color Doppler, respectively) confirm the above results also in the setting of perfusion abnormalities.*

- 3 *The authors report that "CEUS has the potential to compensate for limitations of conventional Doppler modes with a diagnostic performance comparable or superior to CT in detection of perfusion abnormalities, lesion characterization as cystic or solid": until RCT are available it is often restricted only in high experienced centers. We agree with the reviewer. However, despite the lack of randomized trials, the experience acquired in reference centres and guidelines recommendations (e.g., EFSUMB ones) are now promoting an ever-increasing and widespread use of CEUS, as exemplified by extended indications to paediatric population. We also believe that our study results might contribute as a reference for the planning of future studies designed to obtain high-level evidence. In accordance with the reviewer's suggestion, we added the following sentence in the Discussion, when commenting potential cost-effectiveness of CEUS: "One might argue that the use of CEUS is often limited to experienced centers, and no randomized controlled trials support the above statements. However, the experience acquired in reference centres and guidelines recommendations (e.g., EFSUMB ones) are now promoting an ever-increasing and widespread use of CEUS, as exemplified by extended indications to paediatric population^[1]. We also believe that our study results might contribute as a reference for the planning of future studies designed to obtain high-level evidence in large populations with normal or impaired renal function".*

- 4 *renal biopsy was reported to be done in 6% of patients: however, this diagnostic procedure is not usually executed in the clinical suspicion of renal cystic or solid lesion characterization nor in renal infarction nor in acute renal failure of suspicious vascular origin, but the indication is especially in proteinuric or rapidly progressive renal failure of unknown origin. Among 20/31 patients a final presumptive diagnosis was reached and*

in three of them a diagnosis of atheroembolic renal disease had positive skin biopsy; however, the diagnosis in such a pathology is often clinical (see reference Scolari F, Ravani P. Atheroembolic renal disease. Lancet. 2010;375(9726):1650-60), sometimes skin biopsy may help in diagnosis, but the role of CEUS in such a microvascular disease involving interlobular and afferent arterioles by cholesterol crystals (as reported by the authors) that are likely too small to be detected with imaging methods may not be considered of first choice, as also noted by the authors. Concerning renal biopsy, we believe our results are in line with the reviewer's observations, since biopsy was performed in those patients in whom CEUS reasonably excluded a vascular origin for renal failure. Concerning atheroembolic disease, we agree on the fact that diagnosis in clinical in nature, though far from being easy. In our experience, CEUS can significantly contribute to diagnosis in older patients with arteriopathic disease with inconclusive skin biopsy. We believe that, though CEUS might be not conclusive in this setting, it might be of help in patients with suspicious atheroembolic disease, as emphasized by our results.

- 5 The costs of CEUS are cited by the authors but the question remains if an effective method used by experienced hands, like CEUS, avoids further second level exams, much more expensive, both economically and clinically. We agree with the reviewer. On the other hand, we believe these observations are difficult to be applied in the scenario of patients with renal failure, in which – in practical terms – there are no second-level examinations after CEUS: i) CT cannot be used because of the risk of CIN; ii) MRI can be unavailable, costs more than CEUS and is associated with the above concerns on the use of gadolinium contrast media (see point # 1).

- 6 minor grammatical mistakes. Please, see point # (1) above.

- 7 indication to CEUS in this scenario is based more on theoretical considerations and expert opinion than on results of validation studies→ I agree with this conclusion as addressed by the authors. Thank you.

- 8 I agree with Girometti et al that CEUS is a safe, simple, and highly repeatable examination method, and it has broad prospects for future development and application. Prospective randomized controlled trials with larger samples will be needed to confirm the high expectations in the future. Please, see point # 3 for this point (we added dedicated statements in the Discussion).

Thank you again for considering our manuscript for the publication on the *World Journal of Hepatology*.

Sincerely yours,

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