

## Peer Review File

**Article information:** <http://dx.doi.org/10.21037/tp-20-466>

### Reviewer A

**Comment 1:** Line 27 change “resulting” to “result”

**Reply 1:** we have deleted this part.

**Changes in the text:** we have deleted this part.

**Comment 2:** Line 29-30 remove “and the clinical...”

**Reply 2:** we have deleted this part.

**Changes in the text:** we have deleted this part.

**Comment 3:** Line 32-33 The sentence is missing a verb – rephrase

**Reply 3:** we have deleted this sentence in the abstract part and revised it in the method part.

**Changes in the text:** we have deleted this sentence in the abstract part and revised it in the method part (see Page 7, line 130-132).

**Comment 4:** Line 37 Change “A majority” to “The majority”

**Reply 4:** we have modified our text as advised.

**Changes in the text:** we have modified our text as advised. (see Page 3, line 52)

**Comment 5:** Line 39 change “lowered” to “lower”

**Reply 5:** we have deleted this part.

**Changes in the text:** we have deleted this part.

### Reviewer B

#### Major points

**Comment 1:** There is a lack of background information. Since this study shows that MRI is useful in diagnosing NCS from patients with LRV entrapment, it is necessary to describe what is already known about imaging methods for NCS in LRV entrapment. References 5 and 6 mention SMA-angle and CR of CT findings, which should be fully explained in the background if they are to be validated in this study. Also, please add what is already known about DUS in Line 69. This information is essential for comparison with the results of this study, in which MRI can be useful. And then, please clarify how this research is different from those studies. The research hypothesis can also be discussed. Is the expected benefit of MRI only a difference in

modality, i.e., merely avoiding radiation exposure?

**Reply 1:** I quite agree with your point of view and have revised it according to your request. I have added the imaging methods of LRV compression in the “background” and the advantages and disadvantages of the above imaging methods are listed. The high accuracy of SMA-angle, CR and beak sign in diagnosing NCS was explained. The difference between this paper and other papers is that the previous studies on MRI diagnosis of LRV compression in children are relatively few, so this paper is novel and comprehensive.

**Changes in the text:** we add imaging methods for NCS in LRV entrapment(see Page 4, line94-98 ), we add information about SMA-angle, CR and beak sign(see Page5, line104-106), we add information about DUS, CT, MRI, phlebography and intravascular ultrasound(see Page6, line99-112), we clarify how this research is different from those studies(see Page6, line112-115).

**Comment 2:** In Lines 55 to 62, some references need to be added to describe the following points. Please delete unnecessary information and add the necessary information.

” NCS refers to the coexisting of LRV compression and its associated characteristic symptoms, also known as LRV entrapment syndrome.” (Lines 55 to 56),

“It is hypothesized that LRV hypertension may result in hematuria, proteinuria, left flank pain, abdominal pain, and other symptoms associated with nutcracker anatomy.” (Lines 58 to 60)

“The true prevalence of NCS remains unknown, early studies reported that NCS is a rare entity.” (Lines 60 to 61)

“However, an increasing number of patients are being diagnosed after treatment failure for nephropathies.” (Lines 61 to 62)

**Reply 2:** I have added references after the above sentences according to your request.

**Changes in the text:** we add references after the above sentences (see Page5, line79-81, line84-86, line86-87, line 87-88).

**Comment 3:** Please describe the research design clearly. Is this study a retrospective observational study?

**Reply 3:** we have modified our text as advised.

**Changes in the text:** we add “This single-center retrospective study” in the method (see Page6, line120).

**Comment 4:** “Patients with suspected NCS were enrolled in our cohort.” (Line 77)

First of all, please clarify the inclusion criteria and procedures, when, how, and who made the decision. Was NCS suspected from symptoms and urine findings, from

imaging findings, from chart review, by the attending physician, or by the researcher? If these are not clarified, it is impossible to interpret the results correctly. This information is critical in judging group bias and selection bias. Therefore, please describe them clearly.

**Reply 4:** we have added inclusion criteria for suspected nutcracker patients and Flow diagram for inclusion of participants.

**Changes in the text:** we added inclusion criteria for suspected nutcracker patients (see Page7, line126-130) and Flow diagram for inclusion of participants(Figure 1).

**Comment 5:** In this study, patients who were not diagnosed with LRV entrapment must have been excluded, but this is not clearly described.

**Reply 5:** Patients who are not diagnosed with Nutcracker syndrome are usually patients whose radiological examination does not meet the diagnostic criteria for Nutcracker syndrome, or whose left renal vein compression is not severe enough to cause clinical symptoms. These patients were not excluded, but were included in the control group. This grouping method is supported by relevant references (1).

1. Niu Xiao-Ling,Wu Ying,Hao Sheng et al. Value of micro-proteinuria in combination with ultrasonography of the left renal vein in the diagnosis of orthostatic proteinuria.[J] .Ann Transl Med, 2019, 7: 780.

**Changes in the text:** This has been explained in the article (see Page8, line163-164).

**Comment 6:** If possible, please specify and show the diagram about the followings, How many patients were admitted?

How many patients met the inclusion criteria for suspected NCS (LRV entrapment and clinical symptoms)?

How many patients were diagnosed with LRV entrapment on MRI?

How many patients were diagnosed with NCS based on characteristic symptoms and findings?

**Reply 6:** We have drawn a flow diagram for the inclusion of participants (Figure 1)and explained it in detail in the article.

**Changes in the text:** we added some data in the “Results” (see Page10, line205-217).

**Comment 7:** The main problem with the design of this study is that MRI findings are used to diagnose LRV entrapment at inclusion. In the present study, the subject was limited to patients with LRV entrapment diagnosed by MRI, among whom clinicians diagnosed NCS by symptoms and physical findings. What is the clinical value to find out the useful MRI findings to distinguish NCS among those patients? It is unclear what advantage in clinical practice would be created by identifying NCS with MRI findings, while the clinician can identify it by only clinical symptoms and findings.

Ideally, shouldn't all patients with clinical symptoms and physical or urinary findings suspected of NCS be included? LRV entrapment and NCS should be defined based on other well-defined criteria without using MRI, and then MRI findings should be compared among those patients.

**Reply 7:** First of all, thank you very much for your valuable suggestions for the article. Let me explain them one by one.

①What is the clinical value to find out the useful MRI findings to distinguish NCS among those patients? **Re:** In clinical work, diagnosis is the most important. Correct diagnosis can guide the treatment of the disease and determine the prognosis. Misdiagnosis not only delays the treatment of the disease, but also may lead to serious consequences. It is well known that a large proportion of children with renal disease suffer from simple microscopic hematuria, with some patients having a good prognosis and others progressing to end-stage renal disease. Therefore, it is important to clarify their diagnosis. One study (2) found that a large proportion of patients with simple microscopic hematuria were caused by compression of the LRV. Therefore, the use of MRI to distinguish NCS from other diseases can clarify the diagnosis of such patients and better guide the treatment and prognosis of patients.

2. Kurklinsky, A.K. and T.W. Rooke, Nutcracker phenomenon and nutcracker syndrome. *Mayo Clin Proc*, 2010. 85(6): p. 552-9.

②It is unclear what advantage in clinical practice would be created by identifying NCS with MRI findings, while the clinician can identify it by only clinical symptoms and findings. **Re:** Although most patients with NCS have mild clinical symptoms and do not require specific treatment, some patients have more severe symptoms and may require surgery to ameliorate compression of the left renal vein. Although the clinician may suspect compression of the LRV based on the patient's clinical symptoms and signs, it is not possible to make a diagnosis and understand the degree of compression. So MRI can be used not only to diagnose NCS but also to understand the degree of compression of the LRV.

③Ideally, shouldn't all patients with clinical symptoms and physical or urinary findings suspected of NCS be included? **Re:** Our study also included all patients with suspected NCS. Patients with hematuria and/or proteinuria from other causes were then excluded. According to the diagnosis of Nutcracker syndrome, the patients were divided into two groups: Nutcracker group and control group. The inclusion process of research subjects has been pointed out in "Comment 6".

④LRV entrapment and NCS should be defined based on other well-defined criteria without using MRI, and then MRI findings should be compared among those patients.

**Re:** Currently, there is no definite diagnostic criteria for NCS.

**Changes in the text:** There is no change in the article.

**Comment 8:** The gold standard for diagnosis is unclear. Two radiologists reviewed the MRI, and LRV entrapment and NCS were diagnosed by two nephrologists (Lines 88 to 90). How was the concordance rate for each result? If they were not matched, how did they decide the final diagnosis of LRV entrapment or NCS? Please describe clearly.

**Reply 8:** We added the "gold standard" in the introduction. We have described in detail the methods used by two radiologists and two nephrologists to diagnose LRV compression and NCS.

**Changes in the text:** We added the "gold standard" in the introduction (see Page6, line101-103). We added an explanation in the Methods section (see Page8, line158-163).

**Comment 9:** Please explain in detail how to set the angle and CR cut-off.

**Reply 9:** The optimal cut-off value is the point closest to the upper left corner of the ROC curve, where sensitivity and specificity are high and false positives and false negatives are minimal, so as to obtain the cut-off value of the SMA angle and CR.

**Changes in the text:** We have added the above content in the Statistical Analysis section (see Page 10, line199-202).

**Comment10:** The structure of the discussion requires significant revision. The purpose of this study is to show that MRI findings of SMA angle $<36.8^\circ$ , beak sign, and CR $>3.99$  are useful in the diagnosis of NCS from patients with LRV entrapment. The current discussion is inappropriate for drawing this conclusion.

**Reply 10:** We have changed the conclusion section to "Children with SMA angles less than  $36.8^\circ$ , beak signs and CR greater than 3.99 should be highly suspected of having NCS. Among these parameters, "beak sign" showed the highest diagnostic accuracy by MRI, and the combination of any two of the above parameters achieved a higher specificity than the single parameters."

**Changes in the text:** we have modified our text as advised (see Page 4, line 61-64 and Page 14-15, line 317-322)

**Comment 11.** First, the characteristics of the NCS patient group and the review of previous literature are not necessary for the discussion. These should be summarized in the Background section, or the different backgrounds should be described in the Limitation as selection bias.

**Reply 11:** we have deleted this part.

**Changes in the text:** we have deleted this part.

**Comment 12:** The first paragraph, the purpose of this study, should be moved to the background and summarized; the statement that MRI and CT are equivalent needs reference and evidence.

**Reply 12:** we have deleted the first paragraph of the discussion section. We have inserted a reference in the section” the statement that MRI and CT are equivalent”.

**Changes in the text:** we have deleted the first paragraph of the discussion section. We inserted a reference at the end of the sentence “Significant results shown by MRI were very similar to those shown by 3D-CT, with similar accuracy” (see Page5, line 109-111).

**Comment 13:** “In this retrospective study, it was equally prevalent among both genders. Most previous studies have shown a higher proportion of patients in females, especially during pregnancy [3, 10, 11]. However, a study reported that there was no gender difference in the NCS [4].” (Lines 198 to 200)

This part does not seem to be related to the purpose and conclusion of this study. If authors want to provide information about selection bias, please describe it briefly as a limitation.

**Reply 13:** we have deleted this part.

**Changes in the text:** we have deleted this part.

**Comment 14:** “Another factor was associated with NSC is BMI, a low BMI has been proved to correlate positively with NCS [13], which is consistent with the findings of this study.” (Lines 204 to 205)

Please check the grammar in this sentence. Also, how does the fact that the results were similar to previous studies relate to this study's conclusion, i. e., the usefulness of MRI findings? If it is not relevant, it is unnecessary to mention it in the discussion.

**Reply 14:** we have deleted this part.

**Changes in the text:** we have deleted this part.

**Comment 15:** Lines 207 to 224.

This part is only a review of previous studies; it should be summarized in the Introduction or deleted.

**Reply 15:** we have deleted this part.

**Changes in the text:** we have deleted this part.

**Comment 16:** Lines 226 to 239.

This paragraph should be the core of the discussion in this article, but this study's usefulness cannot be understood from that description. Please discuss how and why the results of this study differ from the results of previous studies. Furthermore, please describe for what points this study is useful.

**Reply 16:** we have modified our text as advised.

**Changes in the text:** we have modified our text as advised (see Page 13-14, line 292-307).

**Comment 17:** If the authors want to discuss the usefulness of MRI, it is essential to compare the results with those of other studies using different modalities.

**Reply 17:** we have modified our text as advised. However, the content of this part is relatively small due to the relatively few related researches. Some are also listed in the introduction section.

**Changes in the text:** we have modified our text as advised (see Page 13-14, line 292-307 and Page 4-5 line 99-112).

**Comment 18:** Lines 241 to 246

This part is only a repetition of the Results section and is inappropriate for discussion.

**Reply 18:** we have deleted this part.

**Changes in the text:** we have deleted this part.

**Comment 19:** Limitations are not mentioned. Please summarize it in the last paragraph of the discussion. Limitations may include the description of population and selection bias due to hospital and patient characteristics, retrospective observational study, and the fact that the AUC was calculated only for the target population. External validation was not conducted.

**Reply 19:** We have added the limitation part as required.

**Changes in the text:** we added a limitation section to the discussion (see Page 14, line 308-315).

### **Minor points**

**Comment 1:** There is insufficient information on study design, setting, and statistical analysis in the title and abstract. It is not clear if it is a single-center or prospective study; the STARD checklist also mentions that these should be included.

**Reply 1:** we have added the above information to the abstract.

**Changes in the text:** we added the above information to the abstract (see Page 2, line 44-51).

**Comment 2:** The abstract should include a brief description of the inclusion criteria for suspected NCS, including symptoms and findings.

**Reply 2:** we added the inclusion criteria for suspected NCS to the abstract.

**Changes in the text:** we added the inclusion criteria for suspected NCS to the abstract (see Page 2, line 46-47).

**Comment 3:** All abbreviations should be spelled out at the first occurrence of the text.

NCS, OP, DUS, BMI, etc...

**Reply 3:** we have modified our text as advised.

**Changes in the text:** we have modified our text as advised.

**Comment 4:** Study design is not described in the Methods section.

**Reply 4:** we have added study design in the Method section.

**Changes in the text:** we have added study design in the Method section (see Page 7, line 149-168).

**Comment 5:** "Exclusion of primary or secondary kidney diseases, infectious, toxins, urolithiasis, malignancies, and other diseases that might lead to hematuria and/or proteinuria." (Lines 79 to 80.)

Please check the grammar in this sentence.

**Reply 5:** we have already revised.

**Changes in the text:** we have already revised (see Page 6, line 130-132).

**Comment 6:** There is no description of the sample size.

**Reply 6:** The sample size is described in the Results section.

**Changes in the text:** We have added a description of sample size in the Results section (see Page 9, line 205-208).

**Comment 7:** In Tables 1 and 2,  $p=0.000$  should be  $p<0.001$ . In Table 2, please spell out AM in the footnote.

**Reply 7:** we have modified our text as advised.

**Changes in the text:** we have modified our text as advised (see Table 1 and Table 2).

**Comment 8:** The words "larger" and "smaller" are written in lines 186 to 187. What did the authors compare?

**Reply 9:** This is a comparison of the DUS characteristics of children versus adults. This section has been deleted.

**Changes in the text:** This section has been deleted.

**Comment 9:** "Younger children who could not cooperate with the MRI were excluded" (Lines 202 to 203)

This information should be provided as exclusion criteria in the Methods section.

**Reply 9:** we have modified our text as advised.

**Changes in the text:** we have modified our text as advised (see Page 7, line 137).