OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

Iranian Journal of Pediatrics
Article DOI: 10.5812/ijp.101302
Published in: Iranian Journal of Pediatrics: 30(5); e101302

Peer Review Report for "Predictors of Acute Pyelonephritis in Infants Less Than 4 Months Old with Febrile Urinary Tract Infection"

Author(s): Tung-Yu Lin, Chih-Chieh Yang, Nai-Wen Fang, Jenn-Tzong Chang, Hsiao-Ping Wang , Yee-Hsuan Chiou

Review Timeline:

Submit Date: 26 Jan 2020
Revised Date: 27 Jun 2020
Accepted Date: 16 Jul 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Mehmet Tekin: Reviewer | **Revision** (0) — 15 Feb 2020

Dear AE,
I congratulate the authors. It's a well-written article. I think the article can be published.
Thanks.

REFEREE: Reviewer | **Revision** (0) — 6 Mar 2020

Dear AE,
The study was about the prediction of pyelonephritis in infants younger than 4 months of age with laboratory parameters. The gold standard DMSA was also used in all patients. The cases with hypoactivity in DMSA on those without were compared in terms of laboratory findings. A cut-off value of 4.21 mg/dL was defined as a predictor for APN in the study group.
First the study design:
- I wonder whether DMSA was performed in infants younger than 1 month.
- How was the reduced cortical vascularity defined with USG? Was that power Doppler?
- Did you need to change the antibiotics in any of your patients? Was any of your patients resistant to the antibiotics you gave at the first step? This would also change the response

time in your patients.
- You would better define the percent of your patients defined with catheterization and clean catch urine in your groups. The technique would change the results.
- Since this was a retrospective study, did you determine vesicoureteral reflux in these patients (esp Grade 3-5 VUR).
Tables:
You would better use the same columns in your consecutive tables. The first columns for APN and the second columns for non-APN or vice versa.
“Confidence interval” may be abbreviated or written in full in all tables.
Table 1:
- You might better indicate the minimum and maximum values of the parameters in the table. Indeed I really wonder about the youngest and the oldest patients. How old is the youngest patient receiving DMSA?
- The abbreviations should be written in the order that appears in the table.
- “Escherichia coli” should be written in Italics.
Table 3:
- Area or area under the curve?
Table 4:
- “UVJ, ureterovesical junction” is not required.
References:
You mentioned the predictivity of NLR of reflux. You may mention the predictivity of CRP for reflux either. You may add the following references.
- Soylu A, Kasap B, Demir K, Türkmen M, Kavukçu S. Predictive value of clinical and laboratory variables for vesicoureteral reflux in children. Pediatr Nephrol. 2007 Jun;22(6):844-8. Epub 2007 Feb 2. PubMed PMID: 17273861.
- Bahat H, Ben-Ari M, Ziv-Baran T, Neheman A, Youngster I, Goldman M. Predictors of grade 3-5 vesicoureteral reflux in infants ≤ 2 months of age with pyelonephritis. Pediatr Nephrol. 2019 May;34(5):907-915. DOI: 10.1007/s00467-018-4167-0. Epub 2018 Dec 26. PubMed PMID: 30588547.
Thanks.

REFEREE: Associate Editor | **Revision** (0) 9 Mar 2020

Dear EIC,
The manuscript was reviewed by our reviewers. The reviewers have raised concerns regarding the manuscript, and therefore, the paper is not acceptable for publication in this format. However since the reviewers do find some merit in the paper, I would be willing to reconsider if they wish to undertake major revisions and re-submit, addressing the referees' concerns.
Please note that resubmitting your manuscript does not guarantee acceptance, and that your resubmission will be subject to a re-review before a decision is rendered.
Thanks.

REFEREE: EIC | **Revision** (0) 9 Mar 2020

Dear Author,
Thank you for submitting your manuscript to Iran J Pediatr. Your manuscript has now been

reviewed by two reviewers and an Associate Editor. I now have the reports of the Referees, which suggest that your manuscript might be suitable for publication following a number of revisions. I attach some reviewer comments and invite you to submit a revised version of your manuscript addressing the points made.

Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Iran J Pediatr | ID: 101302

Title: Predictors of acute pyelonephritis in infants less than 4 months old with febrile urinary tract infections.

We would like to thank the Reviewers for his/her kind expression of appreciation of our original work. In addition, all the authors are truly appreciative for the all Reviewers' effort, and thank the all Reviewers for his/her critical and highly constructive comments on how to improve this manuscript. We are grateful for the opportunity to revise our manuscript; we have endeavored to address the problems indicated by the Reviewers.

Reviewers' Comments:

1. I wonder whether DMSA was performed in infants younger than 1 month.

Response: We thank the Reviewer for indicating this point and giving us an opportunity to clarify it further. In our including data, total 15 patients less than 1 month accepted DMSA exam (age from 4 days to 30days). And there are no complication noted in the record.

Result (line102-105)

According to the DMSA result of 205 patients (age from 4-120days), 107 patients were included in the APN group, and 98 patients were included in the non-APN group. The clinical characteristics and laboratory findings for the APN group were compared with those for the non-APN group; the results are presented in Table 1.

Table 1 Clinical and laboratory parameters between patients with and without renal defects on dimercaptosuccinic acid scans

	Non-APN(98)	APN(107)	P value
Age (day)	68.08±30.56 (4-120)	68.73±29.87 (6-118)	0.878
Male	68(69.3%)	78(72.8%)	0.581
Therapeutic delay time (days)	1.03±0.81 (0.5-5)	1.15±0.82 (0.5-3)	0.284
Therapeutic response time (hrs)	8.24±13.95 (0-80)	16.99±17.00 (0-81)	<0.001
Catheterization	11(11.2%)	11(10.3%)	0.828
Resistance*	34 (34.6%)	38 (35.5%)	0.903
WBC (cells/mm^3)	15162±5590 (5140-37440)	16038±5626 (5400-33400)	0.265
NLR	1.31±0.92(0.05-5.69)	1.89±1.14(0.15-5.33)	<0.001
CRP (mg/dL)	3.23±2.87(0.20-11.22)	6.55±4.16(0.95-20.06)	<0.001

VUR	4/30(13.3%)	34/90(34.4%)	0.028
Bacteremia	2(2.0%)	5(4.6%)	0.431
Escherichia coli bacteriuria	92(93.8%)	103(96.2%)	0.302

Values are presented as mean ± standard deviation or percentage (%)
APN, acute pyelonephritis; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein; VUR, vesicoureteral reflux
*Resistance to initial antibiotics according to the minimum inhibitory concentration of urine culture.

2. How was the reduced cortical vascularity defined with USG? Was that power Doppler?

Response: We thank the Reviewer for indicating the unclear point. The kidney sonography with power Doppler was performed by radiologist or pediatric nephrologist. The result of reduced cortical vascularity was defined by their individual clinical judgement.

3. Did you need to change the antibiotics in any of your patients? Was any of your patients resistant to the antibiotics you gave at first step. This would also chance the response time in your patients.

Response: We thank the Reviewer for indicating the unclear point. In our hospital, cefazolin and gentamycin were prescribed as first line empirical antibiotics. These empirical antibiotics are recommended by previous study in Taiwan [1]. We would shift the antibiotic according to the minimum inhibitory concentration (MIC) of urine culture. In total 72 patients of resistant cases, 34 patients were in the non-APN group and 38 patients were in the APN group. And the distribution was non-significant (Table1). Besides, we analyzed our including data and the initial antibiotics of 72 patients are resistant to the MIC of urine culture. But therapeutic response time had no significant finding (Supplemental Table). Therefore, therapeutic response time seems not to be influenced by the antibiotic resistance in our study. The finding also presented at other journal and this possibly due to higher drug concentration in the urine than in the blood and the change of MIC range in Clinical and Laboratory Standards Institute guideline [2].

Result (line 106-109)

Both groups predominantly included male patients, but no significant difference was noted (P = 0.581). The TDT, resistance to initial antibiotics, method of urine

collection, and urine culture pathogen did not differ significantly between the two groups.

Table 1 Clinical and laboratory parameters between patients with and without renal defects on dimercaptosuccinic acid scans

	Non-APN(98)	APN(107)	P value
Age (day)	68.08±30.56 (4-120)	68.73±29.87 (6-118)	0.878
Male	68(69.3%)	78(72.8%)	0.581
Therapeutic delay time (days)	1.03±0.81 (0.5-5)	1.15±0.82 (0.5-3)	0.284
Therapeutic response time (hrs)	8.24±13.95 (0-80)	16.99±17.00 (0-81)	<0.001
Catheterization	11(11.2%)	11(10.3%)	0.828
Resistance*	34 (34.6%)	38 (35.5%)	0.903
WBC (cells/mm^3)	15162±5590 (5140-37440)	16038±5626 (5400-33400)	0.265
NLR	1.31±0.92(0.05-5.69)	1.89±1.14(0.15-5.33)	<0.001
CRP (mg/dL)	3.23±2.87(0.20-11.22)	6.55±4.16(0.95-20.06)	<0.001
VUR	4/30(13.3%)	34/90(34.4%)	0.028
Bacteremia	2(2.0%)	5(4.6%)	0.431
Escherichia coli bacteriuria	92(93.8%)	103(96.2%)	0.302

Values are presented as mean ± standard deviation or percentage (%)

APN, acute pyelonephritis; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein; VUR, vesicoureteral reflux

*Resistance to initial antibiotics according to the minimum inhibitory concentration of urine culture.

Supplemental Table Therapeutic response time between non-resistance and resistance

	Non- Resistance (133)	Resistance (72)	P value
Therapeutic response time (hrs)	13.89±17.12	10.80±14.17	0.192

Referance:

1. WU, Chan-Yao, et al. Childhood urinary tract infection: a clinical analysis of 597 cases. Acta paediatrica Taiwanica. 2004; 45(6): 328-333.

2. CHEN, Pei-Chun, et al. Drug susceptibility and treatment response of common urinary tract infection pathogens in children. Journal of Microbiology, Immunology and Infection. 2014; 47(6): 478-483.

4. You would better define the percent of your patients defined with catheterization and clean catch urine in your groups. The technique would change the results.

Response: We thank the Reviewer for indicating the unclear point and giving us an opportunity to explain it further. In our including data, 11 patients (10.3%) in the APN group and 11 patients (11.2%) in the non-APN group collect urine sample with catheterization (P=0.828). Most of our patient's parents prefer clean catch urine than catheterization. Catheterization would be performed by attending physicians order or difficult collection of midstream clean-catch. The definition of UTI in our article is positive urine culture results (a single organism ≥100,000 colony-forming units/mL for midstream clean-catch collection or ≥10,000 colony-forming units/mL for catheterization) and meets the standard of Pediatric [3].

Reference:

3. Representatives L. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. Pediatrics. 1999; 103(4):843-852.

Result (line 106-109)

Both groups predominantly included male patients, but no significant difference was noted (P = 0.581). The TDT, resistance to initial antibiotics, method of urine collection, and urine culture pathogen did not differ significantly between the two groups.

Table 1 Clinical and laboratory parameters between patients with and without renal defects on dimercaptosuccinic acid scans

	Non-APN(98)	APN(107)	P value
Age (day)	68.08±30.56 (4-120)	68.73±29.87 (6-118)	0.878
Male	68(69.3%)	78(72.8%)	0.581
Therapeutic delay time (days)	1.03±0.81 (0.5-5)	1.15±0.82 (0.5-3)	0.284
Therapeutic response time (hrs)	8.24±13.95 (0-80)	16.99±17.00 (0-81)	<0.001
Catheterization	11(11.2%)	11(10.3%)	0.828
Resistance*	34 (34.6%)	38 (35.5%)	0.903
WBC (cells/mm^3)	15162±5590 (5140-37440)	16038±5626 (5400-33400)	0.265
NLR	1.31±0.92(0.05-5.69)	1.89±1.14(0.15-5.33)	<0.001

CRP (mg/dL)	3.23±2.87(0.20-11.22)	6.55±4.16(0.95-20.06)	<0.001
VUR	4/30(13.3%)	34/90(34.4%)	0.028
Bacteremia	2(2.0%)	5(4.6%)	0.431
Escherichia coli bacteriuria	92(93.8%)	103(96.2%)	0.302

Values are presented as mean ± standard deviation or percentage (%)
APN, acute pyelonephritis; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein; VUR, vesicoureteral reflux
*Resistance to initial antibiotics according to the minimum inhibitory concentration of urine culture.

5. Since this was a retrospective study, did you determine versicoureteral reflux in these patients (esp Grade 3-5 VUR).

Response: We thank the Reviewer for indicating this point and giving us an opportunity to clarify it further. In our hospital, vesicoureteral reflux(VUR) was diagnosed by voiding cystourethrogram (VCUG) or direct radionuclide cystography (DRC) examination. The VUR survey would be recommended to the family if the patient was diagnosed of APN or at recurrent febrile UTI episode. In the APN group, 90 patients (84.1%) accepted VUR survey. There is 31 patients (34.4%) had diagnosed of VUR, and 29 patients had grade 3-5 VUR. Incidence rate was similar to other studies [4, 5]. For the non-APN group, we didn't perform VUR survey regularly and most parents hesitate this exam due to catheterization. In the non-APN group, 30 patients (30.6%) accepted VUR survey. There is 4 patients (13.3%) had diagnosed of VUR, and 2 of them had grade 3 VUR. The incidence rate between the two groups is significant (P=0.028), and other studies also have the same finding [4-6].

Reference:

4. Han, Song Yi, et al. Usefulness of neutrophil-lymphocyte ratio in young children with febrile urinary tract infection. Korean journal of pediatrics. 2016; 59(3): 139.
5. Pokrajac, Danka, Irmina Sefic-Pasic, and Amela Begic. Vesicoureteral reflux and renal scarring in infants after the first febrile urinary tract infection. Medical Archives. 2018; 72(4): 272.
6. Zhang X, Xu H, Zhou L, Cao Q, Shen Q, Sun L, et al. Accuracy of early DMSA scan for VUR in young children with febrile UTI. Pediatrics. 2014; 133(1):e30-e38.

Materials and methods (line 74-76)

The diagnosis of APN is focal decreased uptake at least two views [17]. The diagnosed of vesicoureteral reflux (VUR) is based on voiding cystourethrogram

(VCUG) or direct radionuclide cystography (DRC) examination.

Result (line 108-112)

The TDT, resistance to initial antibiotics, method of urine collection, and urine culture pathogen did not differ significantly between the two groups. In the APN group, 90 patients (84.1%) accepted VUR survey and 31 patients (28.9%) had diagnosed of VUR. In the non-APN group, 30 patients (34.4%) accepted VUR survey and only 4 patients (13.3%) had diagnosed of VUR. The incidence rate of VUR is higher in APN group (P=0.028).

Discussion (line 126-132)

UTI is a common bacterial infection in infants. It causes irreversible renal damage when it progresses to APN. Timely medication administration and adequate antibiotic duration can considerably improve the disease outcome. In our study, patients in APN group have higher incidence rate of VUR. Wu et. al. reviwed 597 infants younger than 1 years old and revealed a positive DMSA renal scan result was a good indicator for prediction the possibility of VUR in UTI patients. It is important to pick up the patients who had APN in UTI patients.

Table 1 Clinical and laboratory parameters between patients with and without renal defects on dimercaptosuccinic acid scans

	Non-APN(98)	APN(107)	P value
Age (day)	68.08±30.56 (4-120)	68.73±29.87 (6-118)	0.878
Male	68(69.3%)	78(72.8%)	0.581
Therapeutic delay time (days)	1.03±0.81 (0.5-5)	1.15±0.82 (0.5-3)	0.284
Therapeutic response time (hrs)	8.24±13.95 (0-80)	16.99±17.00 (0-81)	<0.001
Catheterization	11(11.2%)	11(10.3%)	0.828
Resistance*	34 (34.6%)	38 (35.5%)	0.903
WBC (cells/mm^3)	15162±5590 (5140-37440)	16038±5626 (5400-33400)	0.265
NLR	1.31±0.92(0.05-5.69)	1.89±1.14(0.15-5.33)	<0.001
CRP (mg/dL)	3.23±2.87(0.20-11.22)	6.55±4.16(0.95-20.06)	<0.001
VUR	4/30(13.3%)	34/90(34.4%)	0.028
Bacteremia	2(2.0%)	5(4.6%)	0.431
Escherichia coli bacteriuria	92(93.8%)	103(96.2%)	0.302

Values are presented as mean ± standard deviation or percentage (%)

APN, acute pyelonephritis; WBC, white blood cell; NLR, neutrophil/lymphocyte

ratio; CRP, C-reactive protein; VUR, vesicoureteral reflux

*Resistance to initial antibiotics according to the minimum inhibitory concentration of urine culture.

6. Tables:

You would beter use the same columns in your consecutive tables. The first columns for APN and second columns for non-APN or vice versa.

“Confidence interval” may be abbreviated or written in full in all tables.

Table 1:

- You might better indicate the minimum and maximum values of the parameters in the table. In deed I reaaly wonder the youngest and the oldest patients. How old is the youngest patient receiving DMSA.
- The abbreviations should be written in the order that appear in the table.
- “Escherichia coli” should be written in Italics.

Table 3:

- Area or area under the curve?

Table 4:

- “UVJ, ureterovesical junction” is not required.

Response: We thank the Reviewer for providing the constructive suggestions. We had revised the tables as Reviewer’s valuable advice.

Table 1 Clinical and laboratory parameters between patients with and without renal defects on dimercaptosuccinic acid scans

	Non-APN(98)	APN(107)	P value
Age (day)	68.08±30.56 (4-120)	68.73±29.87 (6-118)	0.878
Male	68(69.3%)	78(72.8%)	0.581
Therapeutic delay time (days)	1.03±0.81 (0.5-5)	1.15±0.82 (0.5-3)	0.284
Therapeutic response time (hrs)	8.24±13.95 (0-80)	16.99±17.00 (0-81)	<0.001
Catheterization	11(11.2%)	11(10.3%)	0.828
Resistance*	34 (34.6%)	38 (35.5%)	0.903
WBC (cells/mm^3)	15162±5590 (5140-37440)	16038±5626 (5400-33400)	0.265
NLR	1.31±0.92(0.05-5.69)	1.89±1.14(0.15-5.33)	<0.001
CRP (mg/dL)	3.23±2.87(0.20-11.22)	6.55±4.16(0.95-20.06)	<0.001
VUR	4/30(13.3%)	34/90(34.4%)	0.028
Bacteremia	2(2.0%)	5(4.6%)	0.431
Escherichia coli bacteriuria	92(93.8%)	103(96.2%)	0.302

Values are presented as mean ± standard deviation or percentage (%)
APN, acute pyelonephritis; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein; VUR, vesicoureteral reflux
*Resistance to initial antibiotics according to the minimum inhibitory concentration of urine culture.

Table 2 Multiple logistic regression analysis of fever pattern and laboratory parameters associated with renal defects on dimercaptosuccinic acid scans

	P value	Odd ratio	95% CI	
			Lower	Upper
WBC	0.375	1.000	1.000	1.000
NLR	0.003	1.675	1.185	2.368
CRP	<0.001	1.340	1.191	1.507
TRT (hrs)	0.004	1.034	1.011	1.057

CI, confidence interval; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein

Table 3 Receiver operating characteristic curve of fever pattern and inflammatory markers associated with renal defects on dimercaptosuccinic acid scans

	AUC	Std. Error	P value	95% CI	
				Lower	Upper
WBC	0.547	0.040	0.240	0.469	0.626
NLR	0.668	0.038	<0.001	0.594	0.742
CRP	0.774	0.032	<0.001	0.711	0.838

AUC, Area under the Curve; CI, confidence interval; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein

Table 4 Renal ultrasonography finding between patients with and without renal defects on dimercaptosuccinic acid scans

	Non-APN(98)	APN(107)	P value
Involved kidney size (cm)	5.30±0.45 (4.0-6.3)*	5.59±0.57(4.2-7.2)	<0.001
Non-involved kidney size (cm)		5.38±0.49(4.2-6.8)	0.215
Hydronephrosis	4(4.1%)	10(9.3%)	0.137
Reduced cortical vascularity	4(4.1%)	25(23.4%)	<0.001

Values are presented as mean ± standard deviation or percentage (%)
APN, acute pyelonephritis

* The mean length of bilateral kidneys in the non-APN group.

7. References:

You mentioned predictivity of NLR of reflux. You may mention the predictivity of CRP for reflux either. You may add the following references.

- Soylu A, Kasap B, Demir K, Türkmen M, Kavukçu S. Predictive value of clinical and laboratory variables for vesicoureteral reflux in children. Pediatr Nephrol. 2007 Jun;22(6):844-8. Epub 2007 Feb 2. PubMed PMID: 17273861.
- Bahat H, Ben-Ari M, Ziv-Baran T, Neheman A, Youngster I, Goldman M. Predictors of grade 3-5 vesicoureteral reflux in infants ≤ 2 months of age with pyelonephritis. Pediatr Nephrol. 2019 May;34(5):907-915. doi: 10.1007/s00467-018-4167-0. Epub 2018 Dec 26. PubMed PMID: 30588547.

Response: We thank the Reviewer for providing the constructive suggestions. We had reviewed these articles and added them to our references.

Discussion

(line 157-161)

Zhang et al. reviewed 21 studies focusing on age groups less than 16 years and illustrated that CRP had moderate accuracy to diagnose APN resulting from UTI (sensitivity: 82.6%, specificity: 66.9%, AUC: 0.81) [12]. Soylu Alper et al. disclosed fever≧ 38 degree C and CRP > 5 mg/dl might be the predictors of VUR and high-grade VUR [23].

(line 167-170)

Han et al. revealed that NLR was higher in the APN group than in the group with simple UTI ($P < 0.001$) among the age group less than 36 months [6]. Other report also indicated higher blood neutrophil percentage and higher NLR are associated with high grade VUR ($P < 0.001$) [27].

8. Associate Editor's Comments:

Your manuscript was reviewed by our reviewers. The reviewers have raised concerns regarding the manuscript, and therefore, your paper is not acceptable for publication in this format. However since the reviewers do find some merit in the paper, I would be willing to reconsider if you wish to undertake major revisions and re-submit, addressing the referees' concerns.

Please note that resubmitting your manuscript does not guarantee acceptance, and that your resubmission will be subject to a re-review before a decision is rendered.

Response: We thank the Associate Editor for giving us an opportunity to clarify these comments. We had revised the article with reviewer's advice. Please contact us if any other comments and problems. In the end, all the authors are appreciative for the constructive comments to improve this manuscript.

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) 11 Jun 2020

Dear AE,
The authors have addressed most of my commnets in a satisfactory way. I have a few points to be cleared out.
1. The authors mentioned that " The diagnosed of vesicoureteral reflux (VUR) is based on voiding cystourethrogram (VCUG) or direct radionuclide cystography (DRC) examination" and
"In the APN group, 90 patients (84.1%) accepted VUR survey. There is 31 patients (34.4%) had diagnosed of VUR, and 29 patients had grade 3-5 VUR. For the non-APN group, we didn't perform VUR survey regularly and most parents hesitate this exam due to catheterization. In the non-APN group, 30 patients (30.6%) accepted VUR survey. There is 4 patients (13.3%) had diagnosed of VUR, and 2 of them had grade 3 VUR."
With direct radionuclide cystography (DRC) method grading of VUR is not possible. If they did not use DRC in their patients they can omit this method. It may be confusing for the readers. If they are sure about the ratios of their patients with VUR, they may include the rate to the manuscript, which would be a valuable finding.
2. The number of patients with VUR and APN was reported as "34" in Table 1. It should be "31" as you mentşoned in the text: "31/90(34.4%)"
3. I am not sure that DMSA is an appropriate examination for a newborn. You mentioned that they had no side effect, but I think you may not observed that yet. I cannot see that you had an institutional review board for the study. You should menton that in the manuscript.
4. Please carefully revise the written English. For example: "There is 31 patients…….
Thanks.

REFEREE: Associate Editor | **Revision** (1) 13 Jun 2020

Dear EIC,
The second round of peer review of the manuscript is completed. I now have the reports of the Referees, which suggest that the manuscript needs more correction.
Thanks.

REFEREE: EIC | **Revision** (1) 13 Jun 2020

Dear Author,

The second round of peer review of your manuscript is completed. I now have the reports of the Referees, which suggest that your manuscript needs more correction.
Thanks.

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Iran J Pediatr | ID: 101302
Title: Predictors of acute pyelonephritis in infants less than 4 months old with febrile urinary tract infections.

We would like to thank the Reviewers for his/her critical and highly constructive comments on how to improve this manuscript. In addition, all the authors are truly appreciative for the all Reviewers' effort, and we have endeavored to address the problems indicated by the Reviewers.

Reviewers' Comments:

1.The authors mentioned that " The diagnosed of vesicoureteral reflux (VUR) is based on voiding cystourethrogram (VCUG) or direct radionuclide cystography (DRC) examination" and "In the APN group, 90 patients (84.1%) accepted VUR survey. There is 31 patients (34.4%) had diagnosed of VUR, and 29 patients had grade 3-5 VUR. For the non-APN group, we didn't perform VUR survey regularly and most parents hesitate this exam due to catheterization. In the non-APN group, 30 patients (30.6%) accepted VUR survey. There is 4 patients (13.3%) had diagnosed of VUR, and 2 of them had grade 3 VUR."
With direct radionuclide cystography (DRC) method grading of VUR is not possible. If they did not use DRC in their patients they can omit this method. It may be confusing for the readers. If they are sure about the ratios of their patients with VUR, they may include the rate to the manuscript, which would be a valuable finding.

Response: We thank the Reviewer for indicating this point and giving us an opportunity to clarify it further. One of our pediatric nephrologists preferred to perform DRC as a screen tool for VUR. If patients who received DRC had positive finding, we would arrange VCUG for the grading of VUR. And we had added the VUR rate in the manuscript and table1.

Materials and methods (line77-78)
The diagnosed of vesicoureteral reflux (VUR) was based on voiding cystourethrogram (VCUG) or direct radionuclide cystography (DRC) examination. If patients who received DRC had positive finding, we would arrange VCUG for the VUR grading.

Result (line111-115)
In the APN group, 90 patients (84.1%) accepted VUR survey and 31 patients (34.4%) had diagnosed of VUR, and 29 patients of them had grade 3-5 VUR. In the non-APN

group, 30 patients (30.6%) accepted VUR survey and only 4 patients (13.3%) had diagnosed of VUR, and 2 of them had grade 3 VUR. The incidence rate of VUR is higher in APN group (P=0.028).

Table 1 Clinical and laboratory parameters between patients with and without renal defects on dimercaptosuccinic acid scans

	Non-APN(98)	APN(107)	P value
Age (day)	68.08±30.56 (4-120)	68.73±29.87 (6-118)	0.878
Male	68(69.3%)	78(72.8%)	0.581
Therapeutic delay time (days)	1.03±0.81 (0.5-5)	1.15±0.82 (0.5-3)	0.284
Therapeutic response time (hrs)	8.24±13.95 (0-80)	16.99±17.00 (0-81)	<0.001
Catheterization	11(11.2%)	11(10.3%)	0.828
Resistance*	34 (34.6%)	38 (35.5%)	0.903
WBC (cells/mm^3)	15162±5590 (5140-37440)	16038±5626 (5400-33400)	0.265
NLR	1.31±0.92(0.05-5.69)	1.89±1.14(0.15-5.33)	<0.001
CRP (mg/dL)	3.23±2.87(0.20-11.22)	6.55±4.16(0.95-20.06)	<0.001
VUR	4/30(13.3%)	31/90(34.4%)	0.028
Bacteremia	2(2.0%)	5(4.6%)	0.431
Escherichia coli bacteriuria	92(93.8%)	103(96.2%)	0.302

Values are presented as mean ± standard deviation or percentage (%)
APN, acute pyelonephritis; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein; VUR, vesicoureteral reflux
*Resistance to initial antibiotics according to the minimum inhibitory concentration of urine culture.

2.

The number of patients with VUR and APN was reported as "34" in Table 1. It should be "31" as you mentioned in the text: "31/90(34.4%)"

Response:

We thank the Reviewer for indicating this mistake. We had corrected it.

Table 1 Clinical and laboratory parameters between patients with and without renal defects on dimercaptosuccinic acid scans

	Non-APN(98)	APN(107)	P value
Age (day)	68.08±30.56 (4-120)	68.73±29.87 (6-118)	0.878
Male	68(69.3%)	78(72.8%)	0.581

Therapeutic delay time (days)	1.03±0.81 (0.5-5)	1.15±0.82 (0.5-3)	0.284
Therapeutic response time (hrs)	8.24±13.95 (0-80)	16.99±17.00 (0-81)	<0.001
Catheterization	11(11.2%)	11(10.3%)	0.828
Resistance*	34 (34.6%)	38 (35.5%)	0.903
WBC (cells/mm^3)	15162±5590 (5140-37440)	16038±5626 (5400-33400)	0.265
NLR	1.31±0.92(0.05-5.69)	1.89±1.14(0.15-5.33)	<0.001
CRP (mg/dL)	3.23±2.87(0.20-11.22)	6.55±4.16(0.95-20.06)	<0.001
VUR	4/30(13.3%)	31/90(34.4%)	0.028
Bacteremia	2(2.0%)	5(4.6%)	0.431
Escherichia coli bacteriuria	92(93.8%)	103(96.2%)	0.302

Values are presented as mean ± standard deviation or percentage (%)
APN, acute pyelonephritis; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein; VUR, vesicoureteral reflux
*Resistance to initial antibiotics according to the minimum inhibitory concentration of urine culture.

3.

I am not sure that DMSA is an appropriate examination for a newborn. You mentioned that they had no side effect, but I think you may not observed that yet. I cannot see that you had an institutional review board for the study. You should mention that in the manuscript.

Response: We thank the Reviewer for indicating the important point and giving us an opportunity to explain it. According to the flow chart, there were no immediate side effects after exam for neonates, like apnea or bradycardia to the sedation course or allergy to Tc-99m. Nuclear medicine procedures exposed relatively low level of ionizing radiation. Other journals also revealed the application and the recommended radioisotope dose of DMSA in the period of neonates [1,2]. But for young individuals, they have higher sensitivity of growing tissues than adults. Younger individuals may have a higher risk for long-term effects from ionizing radiation [1]. But no data was presented in the journal. If concerning the long-term side effects of radioisotope, it really needs further survey in the future. The study had approved by the institutional review board in the Kaohsiung Veterans General Hospital (no.VGHKS19-CT5-06).

References:

1. Treves, S. Ted, et al. "Nuclear medicine in the first year of life." *Journal of Nuclear Medicine* 52.6 (2011): 905-925.
2. Siomou, Ekaterini, et al. "Implications of 99mTc-DMSA scintigraphy performed

during urinary tract infection in neonates." *Pediatrics* 124.3 (2009): 881-887.

Materials and methods (line62-65)

This retrospective study included patients aged less than 4 months with first time febrile UTI between January 2012 and December 2018 at the Kaohsiung Veterans General Hospital, a tertiary referral center in southern Taiwan, and this study had been approved by the institutional review board in the medical center.

Discussion (line138-141)

Moreover, the sedation and radiation risks to young infants should be considered during the DMSA scan. Although our patients who received DMSA had no obvious side effects immediately, young individuals who have higher sensitivity of growing tissues than adults may have a higher risk for long-term effects from ionizing radiation [19].

4.

Please carefully revise the written English. For example: “There is 31 patients…….

Response: We thank the Reviewer for indicating this grammatical mistake. We had rechecked our article carefully. Please refer to our manuscript.

OPEN PEER REVIEW

Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Belde Kasap Demir: Reviewer | **Revision** (2) 16 Jul 2020

Dear AE,
The manuscript may be accepted in its current form.
Thanks.

REFEREE: Associate Editor | **Revision** (2) 16 Jul 2020

Dear EIC,
As the reviewers improved their manuscript based on the reviewer's recommendations, I think it can be accepted.
Thanks.

REFEREE: EIC | **Revision** (2) 16 Jul 2020

Dear Author,
The third round of peer review of your manuscript has been completed, and I am pleased to inform you that your manuscript has now been accepted for publication in our journal.
Thanks.