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OPEN PEER REVIEW

Predictive Value of D-dimer in Children with Acute Pyelonephritis

Sahar Sadr Moharerpour, Leily Mohajerzadeh, Azar Nickavar, Alireza Haghbin Toutounchi

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

2 comments · 9 Apr 2024 – 13 May 2024

Referee 1 Reviewer

MAJOR REVISION 9 Apr 2024

Dear Editor
I have evaluated the manuscript with interest. The inadequacy of the sample size in this study is the main limitation of the study findings and its contribution to the field. The authors should consider the following comments.
1- Please avoid any use of the phrases control group or case-control study in the methods section. The authors should state the study design as a cross-sectional study, not a prospective one.
2- In the methods section, please do not state 2 groups. It would be better to use "study participants" instead. Moreover, state that the study participants were classified into ... using a golden standard test.
2- In the methods section, the authors should explain the methodology for calculating validity measures such as sensitivity.
3- The ROC curve should be revised. Please adjust the position of the legend in the figures.
4- The authors should consider the validity of the D-dimer along with other potential clinical indices and report the relevant AUC. This alternative may increase the strength of prediction.
5- Please report the area under the curve as AUC, not AUCal.
6- The number of citations is eight. Please consider the relevant and appropriate citations in the references.
7- The authors should state the basis for defining the cut-off points.

Banafsheh Arad Reviewer

MINOR REVISION 13 May 2024

1. The whole article is handy and efficient. Some grammar corrections are required.

2. Abstract: In the results section, it is better to use the conjunction “but” instead of “and” in the following sentence: “Binary logistic regression analyses showed that Hgb (P = 0.019) and not serum D-dimer had significant predictive value in APN.”

3. Methods:
- Where was the study conducted?
- What were the sampling methods?
- Please mention the age range of the children.
- Please define the inclusion criteria for the control group precisely. (Where was the source of infection? Was the diagnosis of bacterial infection based on clinical symptoms or laboratory tests?)
- Has VCUG been performed in all patients? Please mention the indications.

4. Results: The results are interesting.
- Please add the age (months) in Table 1.
- What do you mean by D-dimer + VUR in Table 1? (The control group did not have VUR.)
- Is there a relationship between the D-dimer level and vesicoureteral reflux grades?
- Is there a significant difference in the D-dimer level in APN due to E-Coli compared to APN with other bacteria?

5. Discussion: The differences and advantages of this study compared with other studies should be mentioned. Please justify the possible reason for the consistency/inconsistency between the results of the present study and those of previously published studies.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewers' Comments:

Reviewer 1:
Dear Editor
I have evaluated the manuscript with interest. The inadequacy of sample size in this study is the main limitation of the study findings and its contribution to the field. The authors should consider the following comments.

1- Please avoid any use of control group or case-control study phrases in the methods section. The authors should state the study design as a cross-sectional study, not a prospective one.

Reply: This comment was applied to all related sections of the article and highlighted.

2- In the methods section, please do not state 2 groups. It could be better to explain that "study participants". Moreover, state the study participants were classified into ... using a golden standard test.

Reply: This comment was applied to all related sections of the article and highlighted.
2- In the methods section, the authors should explain the methodology of calculation of validity measures such as sensitivity.

Reply: The Youden index (j) method was used which defines the optimal cut-point as the point maximizing the Youden function which is the difference between true positive rate and false positive rate over all possible cut-point values.

3- The ROC curve should be revised. Please adjust the position of the legend in the figures.

Reply: The position of Legends were corrected.

4- The authors should consider the validity of the D-dimer along with other potential clinical indices and report the relevant AUC. This alternative may increase the strength of prediction.

Reply:The validity of clinical parameters with D-dimer were calculated and included in table 5. However, these are qualitative and not quantitative variables, and is not customary to show them.

Variables	Cutoff	Sensitivity	Specificity	AUC	95% CI	Standard Error	P-value
Malodor Urine	382	51.1	69.4	0.578	0.460 - 0.696	0.060	0.193
Urgency	416	69.2	63.2	0.671	0.542 - 0.801	0.066	0.009
Urinary incontinency	386	65.0	52.9	0.570	0.446 - 0.693	0.063	0.269

5- Please report the are under the curve as AUC not AUCal.

Reply: It was corrected.

6- The number of citations is eight. Please consider the relevant and appropriate citations in the references.

Reply: Some references were omitted and New relevant reference was added. Totally, it has to be said, there are few articles related to this topic. To our research, our study was the first to evaluate the value of serum D-dimer for specific diagnosis of urinary tract infection in children, compared with the other bacterial infections.

7- The authors should state what is the basis for defining the cut-off points.

Reply: The approach for determining cut-off points is based on the value of area under the ROC curve. This method defines the optimal cut-point value as the value in which sensitivity and specificity are the closest to the value of the area under the ROC curve and the absolute value of difference between sensitivity and specificity values is minimum.

Reviewer 2:
Comment 1: In line 6, correct the word "results".

Reply: It was corrected.

Comment 2: How did you determine the sample size in each group?

Reply: Sample size was calculated based on the sample size determination formula by comparing the mean of the two populations. Mean and variance values were extracted from the study entitled "D-dimer as a marker of acute pyelonephritis in infants younger than 24 months with urinary tract infection", Reference No 2.

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \times \left(\sigma_1^{\,2} + \sigma_2^{\,2}\right)}{\left(\mu_1 - \mu_2\right)^2}$$

α 0.05 =

β=0.20

$\sigma_1 = 134.3$

$\sigma_2 = 335.5$

$\mu_1 = 258.8$

$$\mu_2 = 403.6$$

$$n = \frac{(1.96+0.84)^2 \times (134.3^2+335.5^2)}{(258.8-403.6)^2} = 48 \qquad \text{for any group}$$

Comment 3: What test did you use to check the normality of the observations? Please mention it in the method section.

Reply: Reply: Normality of data was checked using the Kolmogorov–Smirnov test, and included in the methods section.

Comment 4: Why didn't you use Pearson's correlation coefficient to determine the relationship between two variables?

Reply: It was done and presented as table 4.

Comment 5: It is better to calculate and mention the average temperature of children in each group separately.

Reply: It was calculated and included in table 1.

Comment 6: in line 100, you mean that Hgb level and serum D-diamer were significant variables? why did you report odds ratio and CI just for Hgb level? please report odds ratio and CI for serum D-diamer.

Reply: It was intensified that D-dimer was not an independent predictor of acute pyelonephritis.

Comment 7: Did you enter all variables into the multivariate analysis? What was the reason for univariate analysis?

Reply: First univariate analysis was done . Then multivariate analysis was performed to identify the concurrent effect of all variables on the response variable.

Comment 8: Why did you consider the cut point for some variables where the sensitivity is more than the specificity and vice versa for some variables.

Reply: It is possible to determine the cut off point of a factor in cases with unequal sensitivity and specificity. Following is a sample one: https://doi.org/10.1007/s00467-017-3843-9

Reviewer 3:
1. The whole article is handy and efficient. Some grammar corrections are required.

Reply: Grammatical errors were corrected.

2. Abstract: In the result section, it is better to use the preposition "but instead of and in the following sentence "Binary logistic regression analyses showed that Hgb (P = 0.019) and not serum D-dimer had significant predictive value in APN." *Reply: "Not" was omitted and substituted by "but".*

3. Methods:
- Where was the study conducted?

Reply: It was added in the method section.

- What were the sampling methods?

Reply: Sampling was done randomly.

- Please mention the age range of the children.

Reply: It was added to table 1 and the result section and highlighted.

- Please define the inclusion criteria for the control group precisely. (Where was the source of infection?

Reply: Diagnosis of bacterial infection was based on clinical symptoms and laboratory tests, which added to the methods section

.
- Has VCUG been done in all patients? Please mention the indications.

Reply: Indications of VCUG were explained.

4. Results: The results are interesting.
- Please add the age (month) in Table 1. Reply: Age was presented as month in table 1.

- What do you mean by D-dimer + VUR in Table 1? (The control group did not have VUR).

Reply: This was omitted from table 1.

- Is there a relationship between D-dimer level and vesicoureteral reflux grades?

Reply : According to the kruskal wallis test there was no significant relation between mean serum D-dimer with different grades of reflux (P = 0. 712).

- Is there a significant difference in the D-dimer level in APN due to E-Coli compared to APN with other bacteria?

Reply: As the number of bacteria other than Ecoli was rare, this calculation was not done.

5. Discussion: The differences and advantages of this study should be compared and mentioned with other studies. Please justify the possible reason for the consistency/ inconsistency of the results of the present study and previously published studies.

Reply: This comment was included as far as possible.

Associate Editor's Comments:

Associate Editor 1:
Dear Author
Thank you for sending such a valuable manuscript. There are a few comments regarding your manuscript as following:
Reviewer 1:
1-Please avoid any use of control group or case-control study phrases in the methods section. The authors should state the study design as a cross-sectional study, not a prospective one.
2- In the methods section, please do not state 2 groups. It could be better to explain that "study participants". Moreover, state the study participants were classified into ... using a golden standard test.
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5- Please report the are under the curve as AUC not AUCal.
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7- The authors should state what is the basis for defining the cut-off points.
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Comment 6: in line 100, you mean that Hgb level and serum D-diamer were significant variables? why did you report odds ratio and CI just for Hgb level? please report odds ratio and CI for serum D-diamer.
Comment 7: Did you enter all variables into the multivariate analysis? What was the reason for univariate analysis?
Comment 8: Why did you consider the cut point for some variables where the sensitivity is more than the specificity and vice versa for some variables.
With best regards

2 Revision 1

1 comment · 17 Jul 2024

Referee 1 Reviewer

ACCEPT 17 Jul 2024

The comments raised were considered.

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Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear editorials

Following, please find response to the editorial comments (Changes are highlighted in blue colour):

Comment 1: It's better to use software to determine an efficient sample size.

Reply: Sample size was calculated by version 3.1 GPower software.

Comment 2: Did you select some variables and enter them into the multivariate model?

:Reply

First, the correlation between the independent variables was measured, and from those that were correlated with each other a number of variables were removed, and the other variables were entered into the multivariate model to examine their association with the response variable, which is the disease status.

Comment 3: Please explain how to determine the sample size in the text of the manuscript.

Reply: Sample size was calculated based on comparing mean value of the two populations.

Comment 4: based on results in Table 3, D-dimer had a significant correlation with ESR and Hgb, you shouldn't enter correlated variables in a model.

Reply:

Table 2 was changed and new analysis included.

Comment 5: you should use the same format for the names of variables in whole the text.

Reply: Its was done.

3 Revision 2

0 comments

No public comments in this round.