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Kepada: mahrus.a@fk.unair.ac.id

10 September 2021 pukul 08.31

10-Sep-2021

Dear Dr Rahman:

A manuscript titled Correlation Analysis between Cyanotic Congenital Heart Disease and Nephropathy in Children (DKMJ-2021-002) has been submitted by Dr Mahrus Rahman to the Dokkyo Medical Journal.

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MAHRUS A. <mahrus.a@fk.unair.ac.id>
Kepada: dr.helenwila02@gmail.com

13 September 2021 pukul 15.13

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Dokkyo Medical Journal - Manuscript ID DKMJ-2021-002

2 pesan

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10 September 2021 pukul 08.31

Balas Ke: igakukai@dokkyomed.ac.jp

Kepada: mahrus.a@fk.unair.ac.id

Cc: helenwmt1@gmail.com

10-Sep-2021

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MAHRUS A. <mahrus.a@fk.unair.ac.id>

13 September 2021 pukul 15.13

Kepada: dr.helenwila02@gmail.com

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4 Oktober 2021 pukul 05.51

Balas Ke: isimitu@dokkyomed.ac.jp

Kepada: mahrus.a@fk.unair.ac.id

Cc: helenwmt1@gmail.com

04-Oct-2021

Dear Dr Rahman:

Manuscript ID DKMJ-2021-002 entitled "Correlation Analysis between Cyanotic Congenital Heart Disease and Nephropathy in Children" which you submitted to the Dokkyo Medical Journal, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

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Sincerely,
Toshihiko Ishimitsu
Editor in Chief, Dokkyo Medical Journal
isimitu@dokkyomed.ac.jp

[Reviewer(s)' Comments]

Reviewer: 1

Comments to the Author

- 1) As the indicated data are categorical or bivalent parameters, it is inappropriate to apply the Spearman correlation for the analysis. Chi-square test should be used indicating χ^2 and p values to show the difference in the frequencies between the two groups.
- 2) Page 1: Title should be changed to "Prevalence of nephropathy in children with cyanotic congenital heart disease" for example.
- 3) Page 4, lines 2-3: "Tetralogy of Fallot", "Double outlet right ventricle" >> "tetralogy of Fallot", "double outlet right ventricle" Similar inappropriate use of capital letter has to be corrected throughout the manuscript.
- 4) Page 5, lines 20: "ventricular septal defects (DSV)", "atrial septal defects (DSA)" >> "ventricular septal defects (VSD)", "atrial septal defects (ASD)"
- 5) Page 6, line 2: "anatomical" >> "structural" or "organic"
- 6) Page 7, line 2: "were divided into two groups" >> "consisted of two groups"
- 7) Page 7, lines 8-10: "Each pediatric patient with CCHD and child control participants received written consent from parents or guardians." >> "Written consent was obtained from each pediatric patient with CCHD, child control participants and their parents or guardians."
- 8) Page 7, lines 21-22: "and/or the results of the examination. Urine sediment shows WBC >5/hpf with found bacteria" >> "and/or the urine sediment showed WBC >5/hpf with found bacteria"
- 9) Page 7, line 23-24, page 11, line 4: "angiotensin-converting enzyme (ACE) inhibitors", "Angiotensin-converting enzyme inhibitor (ACEI)" Unify the abbreviations.
- 10) Page 11, line 17: "were in the 4-year period" >> "were 4-year-old or less" ?
- 11) Page 12, line 5: "with the most as many as 104 cases" >> "with as many as 104 cases"
- 12) Page 12, line 12: "erythropoietin stimulation" >> "erythropoietin"
- 13) Page 12, lines 22-23: "Table 3 reported that hematuria in children with CCHD is between the CCHD group and the control group." >> "Table 3 reported that hematuria is more prevalent in the CCHD group than in the control group." ?
- 14) Page 13, lines 6-7: "the incidence of proteinuria in DORV was 9 (52.94%) significantly higher than TOF 8 (47.06%)." >> "the incidence of proteinuria was significantly higher in DORV (52.94%) than in TOF (47.06%)."
- 15) Page 12, line 19: "12 children with positive CHD" >> "12 children with CHD"
- 16) Page 12, line 21 to page 14, line 2: "GFB consists of and cause hematuria [23]." The sentences are repetitive and should be deleted.
- 17) Page 14, line 7: "older children and adults" >> "older children and adults with CHD"
- 18) Page 15, line 4: "the kit found a difference" >> "the results showed a difference"
- 19) Tables 1-4: All the abbreviations used in the Tables have to be explained by full-spelling in the footnotes.

Reviewer: 2

Comments to the Author

This study shows increased urinary abnormalities (positive proteinuria and/or hematuria) frequency in pediatric CCHD patients. This finding does not seem to be completely novel, though intriguingly, the authors suggested some potential difference according to CCHD disease types. As a substantially weak point, there are inadequacies in the overall data. To be accepted for publication, there are a couple points which require improvement. I suggest and encourage so that the authors would revise the manuscript based on the following points.

1.

Is it possible to present graded proteinuria and hematuria (like +1, +2, ---)? If it is possible, that's much preferable. Statistical analyses had better be made based on the graded values.
2.

Notable lacking variables of patient background which should preferably be included as much as possible, may include the following.

heart rate (or pulse rate), presence/absence of arrhythmia, cardiac function indices (such as BNP, EF, PCWP etc), symptomatic HF index (such as NYNA index), presence/absence of history of surgery, body mass index, information about use of HF medication (beta blocker, diuretic etc)

kidney function (creatinine, eGFR), hemoglobin/hematocrit (though authors admit this was unavailable), WBC, platelet, liver function values, glucose, HbA1c, lipids (cholesterol, TG etc), electrolytes (Na, K)
3.

Control subjects were patients of other diseases or healthy people undergoing health checkups? There should be some explanation about the conditions of these subjects including types of diseases.
4.

Please try to make some explanation about the reasons why there were differences in urinary findings between TOF and TORV. This may concern the novelty of this particular study.
5.

For further analysis, I suggest adding graphs comparing the levels sPO2 of proteinuria+ group and proteinuria- group.

P values about the differences should be shown, although they may be either positive or negative. Confidence intervals had better be also indicated in some way (either SD or interquartile). If the authors are willing, dots of all the values could be also added to the graph. This analysis should be also done about blood pressure data, which is also available to the authors.

Same analysis could be also done also about hematuria or proteinuria+ hematuria.

Same analysis can also be tried separately for TOF and TORV, especially if some difference can be found.

If possible, same analysis could also be tried about a couple of other variables (like EF, BNP, HR etc, if available) which are importantly related to hypoxia or cardiac circulatory functions. This may be interesting especially if some difference can be found.

6.

In Table 1, there should be p values for differences of BP, or all other variables compared.

7.

In Table 1, diagnosis percentages (like TOF) had better be shown in a separate table.

8.

In two paragraphs in discussion, there are relatively long sections with the same sentences repeated. (the paragraph on p12 which starts with 'Table 3 reported that hematuria', and the paragraph on p13 which starts with 'Table 4 reports that there are 12 children'. This should be avoided.

MAHRUS A. <mahrus.a@fk.unair.ac.id>
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5 Oktober 2021 pukul 13.28

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Dokkyo Medical Journal - Manuscript ID DKMJ-2021-002.R1

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Dokkyo Medical Journal <onbehalf@manuscriptcentral.com>

12 November 2021 pukul 12.48

Balas Ke: igakukai@dokkyomed.ac.jp

Kepada: mahrus.a@fk.unair.ac.id

Cc: helenwmt1@gmail.com

12-Nov-2021

Dear Dr Rahman:

Your manuscript entitled "Correlation Analysis between Cyanotic Congenital Heart Disease and Nephropathy in Children" has been successfully submitted online and is presently being given full consideration for publication in the Dokkyo Medical Journal.

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27 November 2021 pukul 14.59

Balas Ke: isimitu@dokkyomed.ac.jp

Kepada: mahrus.a@fk.unair.ac.id

Cc: helenwmt1@gmail.com

27-Nov-2021

Dear Dr Rahman: Manuscript ID DKMJ-2021-002.R1 entitled "Correlation Analysis between Cyanotic Congenital Heart Disease and Nephropathy in Children" which you submitted to the Dokkyo Medical Journal, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

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Once again, thank you for submitting your manuscript to the Dokkyo Medical Journal and I look forward to receiving your revision.

Sincerely,
Toshihiko Ishimitsu
Editor in Chief, Dokkyo Medical Journal
isimitu@dokkyomed.ac.jp

[Reviewer(s)' Comments]

Reviewer: 1

Comments to the Author

1) Again, this reviewer recommends to withheld the use of "correlation" because statistically it remind readers of

relationship between the two quantitative parameters and the correlation coefficient should be indicated in order to evaluate its significance. If the authors are reluctant to describe it as "prevalence", this reviewer suggests to use other words such as "relation", "relationship" and "association".

2) Page 7, lines 6-7: "The participants of this study were consisted of two groups," >> "The participants of this study consisted of two groups,"

3) There are four "ACEI" and three "ACE inhibitors". Unify the abbreviations.

4) Page 13, line 7: "DORV (52.94%) than in TOF (47.06%)" >> "DORV (69.23%) than in TOF 28.57%" according to Table 4?

5) Tables 1, 2nd column, 1st row: "CCHD" has to be explained by full-spelling in the footnotes.

6) Table 4, footnotes: Delete "Spearman correlation test were used to determine the correlation coefficient."

Reviewer: 2

Comments to the Author

In this revised manuscript, several improvements have been made concerning inadequacies in the first version. This manuscript, as it is now, may be appropriate for acceptance, but if possible, it may be preferable that a couple of minor points are corrected.

1.

In Table 1, it may be unnatural that p values are not indicated for blood pressure values. Even if there is no statistical significance, these should be indicated. (Or it could be so stated in the Table)

2.

Since most comparisons are made by chi square method, use of "correlation" may be rather inappropriate.

The title could simply be "Association between Cyanotic Congenital Heart Disease and Nephropathy in Children", for example. "Association", which could be used more broadly, may be more natural.

The word "correlation" is basically not appropriate also in other parts of the manuscript.

Dokkyo Medical Journal - Decision on Manuscript ID DKMJ-2021-002.R2

2 pesan

Dokkyo Medical Journal <onbehalf@manuscriptcentral.com>

11 Desember 2021 pukul 14.52

Balas Ke: isimitu@dokkyomed.ac.jp

Kepada: mahrus.a@fk.unair.ac.id

Cc: helenwmt1@gmail.com

11-Dec-2021

Dear Dr Rahman: Manuscript ID DKMJ-2021-002.R2 entitled "Association Analysis between Cyanotic Congenital Heart Disease and Nephropathy in Children" which you submitted to the Dokkyo Medical Journal, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

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Editor in Chief, Dokkyo Medical Journal
isimitu@dokkyomed.ac.jp

[Reviewer(s)' Comments]

Reviewer: 2

Comments to the Author

Still in this version, it may give the impression that Table 1 is uncompleted, lacking some p values. But I regard this acceptable if this is also regarded acceptable by the Editor. I would leave it to the editorial discretion whether further

upgrading is needed or not.

Reviewer: 1

Comments to the Author

There still remain "correlation" in the titles of Table 4 and Table 5.

MAHRUS A. <mahrus.a@fk.unair.ac.id>
Kepada: dr.helenwila02@gmail.com

13 Desember 2021 pukul 10.36

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17-Dec-2021

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Editor in Chief, Dokkyo Medical Journal
Department of Anesthesiology
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13 September 2021 pukul 15.13

Kepada: dr.helenwila02@gmail.com

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Kepada: dr.helenwila02@gmail.com

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4 Oktober 2021 pukul 05.51

Balas Ke: isimitu@dokkyomed.ac.jp

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Cc: helenwmt1@gmail.com

04-Oct-2021

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isimitu@dokkyomed.ac.jp

[Reviewer(s)' Comments]

Reviewer: 1

Comments to the Author

- 1) As the indicated data are categorical or bivalent parameters, it is inappropriate to apply the Spearman correlation for the analysis. Chi-square test should be used indicating χ^2 and p values to show the difference in the frequencies between the two groups.
- 2) Page 1: Title should be changed to "Prevalence of nephropathy in children with cyanotic congenital heart disease" for example.
- 3) Page 4, lines 2-3: "Tetralogy of Fallot", "Double outlet right ventricle" >> "tetralogy of Fallot", "double outlet right ventricle" Similar inappropriate use of capital letter has to be corrected throughout the manuscript.
- 4) Page 5, lines 20: "ventricular septal defects (DSV)", "atrial septal defects (DSA)" >> "ventricular septal defects (VSD)", "atrial septal defects (ASD)"
- 5) Page 6, line 2: "anatomical" >> "structural" or "organic"
- 6) Page 7, line 2: "were divided into two groups" >> "consisted of two groups"
- 7) Page 7, lines 8-10: "Each pediatric patient with CCHD and child control participants received written consent from parents or guardians." >> "Written consent was obtained from each pediatric patient with CCHD, child control participants and their parents or guardians."
- 8) Page 7, lines 21-22: "and/or the results of the examination. Urine sediment shows WBC >5/hpf with found bacteria" >> "and/or the urine sediment showed WBC >5/hpf with found bacteria"
- 9) Page 7, line 23-24, page 11, line 4: "angiotensin-converting enzyme (ACE) inhibitors", "Angiotensin-converting enzyme inhibitor (ACEI)" Unify the abbreviations.
- 10) Page 11, line 17: "were in the 4-year period" >> "were 4-year-old or less" ?
- 11) Page 12, line 5: "with the most as many as 104 cases" >> "with as many as 104 cases"
- 12) Page 12, line 12: "erythropoietin stimulation" >> "erythropoietin"
- 13) Page 12, lines 22-23: "Table 3 reported that hematuria in children with CCHD is between the CCHD group and the control group." >> "Table 3 reported that hematuria is more prevalent in the CCHD group than in the control group." ?
- 14) Page 13, lines 6-7: "the incidence of proteinuria in DORV was 9 (52.94%) significantly higher than TOF 8 (47.06%)." >> "the incidence of proteinuria was significantly higher in DORV (52.94%) than in TOF (47.06%)."
- 15) Page 12, line 19: "12 children with positive CHD" >> "12 children with CHD"
- 16) Page 12, line 21 to page 14, line 2: "GFB consists of and cause hematuria [23]." The sentences are repetitive and should be deleted.
- 17) Page 14, line 7: "older children and adults" >> "older children and adults with CHD"
- 18) Page 15, line 4: "the kit found a difference" >> "the results showed a difference"
- 19) Tables 1-4: All the abbreviations used in the Tables have to be explained by full-spelling in the footnotes.

Reviewer: 2

Comments to the Author

This study shows increased urinary abnormalities (positive proteinuria and/or hematuria) frequency in pediatric CCHD patients. This finding does not seem to be completely novel, though intriguingly, the authors suggested some potential difference according to CCHD disease types. As a substantial weak point, there are inadequacies in the overall data. To be accepted for publication, there are a couple points which require improvement. I suggest and encourage so that the authors would revise the manuscript based on the following points.

1.
Is it possible to present graded proteinuria and hematuria (like +1, +2, ---)? If it is possible, that's much preferable. Statistical analyses had better be made based on the graded values.
2.
Notable lacking variables of patient background which should preferably be included as much as possible, may include the following.

heart rate (or pulse rate), presence/absence of arrhythmia, cardiac function indices (such as BNP, EF, PCWP etc), symptomatic HF index (such as NYNA index), presence/absence of history of surgery, body mass index, information about use of HF medication (beta blocker, diuretic etc)

kidney function (creatinine, eGFR), hemoglobin/hematocrit (though authors admit this was unavailable), WBC, platelet, liver function values, glucose, HbA1c, lipids (cholesterol, TG etc), electrolytes (Na, K)
3.
Control subjects were patients of other diseases or healthy people undergoing health checkups? There should be some explanation about the conditions of these subjects including types of diseases.
4.
Please try to make some explanation about the reasons why there were differences in urinary findings between TOF and TORV. This may concern the novelty of this particular study.
5.
For further analysis, I suggest adding graphs comparing the levels sPO2 of proteinuria+ group and proteinuria- group.

P values about the differences should be shown, although they may be either positive or negative. Confidence intervals had better be also indicated in some way (either SD or interquartile). If the authors are willing, dots of all the values could be also added to the graph. This analysis should be also done about blood pressure data, which is also available to the authors.

Same analysis could be also done also about hematuria or proteinuria+ hematuria.

Same analysis can also be tried separately for TOF and TORV, especially if some difference can be found.

If possible, same analysis could also be tried about a couple of other variables (like EF, BNP, HR etc, if available) which are importantly related to hypoxia or cardiac circulatory functions. This may be interesting especially if some difference can be found.

6.

In Table 1, there should be p values for differences of BP, or all other variables compared.

7.

In Table 1, diagnosis percentages (like TOF) had better be shown in a separate table.

8.

In two paragraphs in discussion, there are relatively long sections with the same sentences repeated. (the paragraph on p12 which starts with 'Table 3 reported that hematuria', and the paragraph on p13 which starts with 'Table 4 reports that there are 12 children'. This should be avoided.

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5 Oktober 2021 pukul 13.28

[Kutipan teks disembunyikan]

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12 November 2021 pukul 12.48

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12-Nov-2021

Dear Dr Rahman:

Your manuscript entitled "Correlation Analysis between Cyanotic Congenital Heart Disease and Nephropathy in Children" has been successfully submitted online and is presently being given full consideration for publication in the Dokkyo Medical Journal.

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Dokkyo Medical Journal Editorial Office

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27 November 2021 pukul 14.59

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27-Nov-2021

Dear Dr Rahman: Manuscript ID DKMJ-2021-002.R1 entitled "Correlation Analysis between Cyanotic Congenital Heart Disease and Nephropathy in Children" which you submitted to the Dokkyo Medical Journal, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some minor revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

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Once again, thank you for submitting your manuscript to the Dokkyo Medical Journal and I look forward to receiving your revision.

Sincerely,
Toshihiko Ishimitsu
Editor in Chief, Dokkyo Medical Journal
isimitu@dokkyomed.ac.jp

[Reviewer(s)' Comments]

Reviewer: 1

Comments to the Author

1) Again, this reviewer recommends to withheld the use of "correlation" because statistically it remind readers of

relationship between the two quantitative parameters and the correlation coefficient should be indicated in order to evaluate its significance. If the authors are reluctant to describe it as "prevalence", this reviewer suggests to use other words such as "relation", "relationship" and "association".

2) Page 7, lines 6-7: "The participants of this study were consisted of two groups," >> "The participants of this study consisted of two groups,"

3) There are four "ACEI" and three "ACE inhibitors". Unify the abbreviations.

4) Page 13, line 7: "DORV (52.94%) than in TOF (47.06%)" >> "DORV (69.23%) than in TOF 28.57%" according to Table 4?

5) Tables 1, 2nd column, 1st row: "CCHD" has to be explained by full-spelling in the footnotes.

6) Table 4, footnotes: Delete "Spearman correlation test were used to determine the correlation coefficient."

Reviewer: 2

Comments to the Author

In this revised manuscript, several improvements have been made concerning inadequacies in the first version. This manuscript, as it is now, may be appropriate for acceptance, but if possible, it may be preferable that a couple of minor points are corrected.

1.
In Table 1, it may be unnatural that p values are not indicated for blood pressure values. Even if there is no statistical significance, these should be indicated. (Or it could be so stated in the Table)

2.
Since most comparisons are made by chi square method, use of "correlation" may be rather inappropriate. The title could simply be "Association between Cyanotic Congenital Heart Disease and Nephropathy in Children", for example. "Association", which could be used more broadly, may be more natural. The word "correlation" is basically not appropriate also in other parts of the manuscript.

Dokkyo Medical Journal - Decision on Manuscript ID DKMJ-2021-002.R2

2 pesan

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11 Desember 2021 pukul 14.52

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11-Dec-2021

Dear Dr Rahman: Manuscript ID DKMJ-2021-002.R2 entitled "Association Analysis between Cyanotic Congenital Heart Disease and Nephropathy in Children" which you submitted to the Dokkyo Medical Journal, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some minor revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

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4. Click "create a revision" on the manuscript you are going to revise.
5. The system creates your revision manuscript form. Provide your comments about the revised points at the response field, fill in on each field step by step as same as you did for the original submission, and submit your revised manuscript.

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Once again, thank you for submitting your manuscript to the Dokkyo Medical Journal and I look forward to receiving your revision.

Sincerely,
Toshihiko Ishimitsu
Editor in Chief, Dokkyo Medical Journal
isimitu@dokkyomed.ac.jp

[Reviewer(s)' Comments]

Reviewer: 2

Comments to the Author

Still in this version, it may give the impression that Table 1 is uncompleted, lacking some p values. But I regard this acceptable if this is also regarded acceptable by the Editor. I would leave it to the editorial discretion whether further

upgrading is needed or not.

Reviewer: 1

Comments to the Author

There still remain "correlation" in the titles of Table 4 and Table 5.

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13 Desember 2021 pukul 10.36

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17-Dec-2021

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