

PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Paediatric Dilated Cardiomyopathy in Khartoum State, Sudan: a prospective study
AUTHORS	Elshazali, osama Hafiz Abdalla, Ekhlas

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Shine Kumar Institution and Country: Amrita Institute of Medical Sciences and Research Centre, Pediatric Cardiology, Kerala, India Competing interests: None
REVIEW RETURNED	17-Dec-2020

GENERAL COMMENTS	<p>Reviewers comments</p> <p>The paper has attempted to describe epidemiology of DCM in an African country. There are significant short comings at various levels. Please find the comments below.</p> <p>Title</p> <p>1. Title does not reflect the content with respect to geographical area. The study is based on data from a single state. It is not clear whether the institutions mentioned are the only referral centers for DCM patients for entire Sudan. If not, it is better to reframe the geographical area depending on the population catered for. Moreover, authors may further expand on the aspects of the disease studied rather than just mentioning "pattern".</p> <p>Abstract</p> <p>2. The aim of study is vague and requires more clarity. Please expand on the word pattern. 3. In results it is mentioned that all 55 were admitted. But in materials and methods its mentioned admission or OPD evaluation. Please clarify. 4. The statement regarding incidence in results is inappropriate. Please refer to comment no 23 under discussion. 5. There is no mention regarding malnutrition in results. Please include the same.</p> <p>Introduction</p> <p>6. Introduction seems appropriate. 7. P5L38-44 – the last line in introduction requires more clarity and refinement. Please clearly state the existing deficiencies.</p> <p>Methodology</p> <p>8. In the objective, the authors have stated that the study applies to Sudan as a whole. However, the study was done in three hospital in a single state. Unless these are the only referral centers for DCM patients for the whole country, it is better to redefine the</p>
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	<p>geographical area catered for by these hospitals. It would be appropriate to describe as institutional experience from a single state. Please clarify this aspect.</p> <p>9. The inclusion and exclusion criteria are not mentioned. Please add them. Please include the criteria used for defining DCM in children with reference.</p> <p>10. Please define the echocardiographic variable used to define LV dysfunction with reference.</p> <p>11. P6L33-35 - this sentence can be deleted once the inclusion and exclusion criteria are clearly mentioned.</p> <p>12. Please modify the statistical methods and mention only the analysis used.</p> <p>13. It is better to mention that diagnosis of post viral myocarditis was purely clinical and no viral studies were done. A standard protocol for work up of DCM if followed should be mentioned.</p> <p>Results</p> <p>14. P8L13-15 - The sentence is confusing. It is better to mention the commonest age group at diagnosis. The age distribution can be mentioned as separate sentence.</p> <p>15. P8L46,47 - Please discuss in detail the familial DCM. The etiology is unclear for the siblings who died and there is no mention of the disease status in parents.</p> <p>16. P8L47,48 - there is mention regarding family history of arrhythmia, but no details available. Please explain the type of arrhythmias, outcomes etc.</p> <p>17. P8L55,56 - Please write in detail regarding those presented with acute heart failure requiring inotropic support rather than just mentioning need for dopamine.</p> <p>18. The outcomes should be written in detail. Age at death, outcomes of various types of DCM etc should be mentioned.</p> <p>19. There is significant proportion of children with malnutrition. But there is no data regarding and nutritional or metabolic data relating to DCM as a cause eg hypocalcemia.</p> <p>20. There is no mention regarding any syndromes associated with DCM.</p> <p>21. The result section should be edited for more comprehensiveness and refinement.</p> <p>22. There is no attempt to delineate risk factors related to mortality. Though numbers are limited, it would be interesting to probe this aspect especially with a background of significant malnutrition.</p> <p>Discussion</p> <p>23. P9L14,15,16 - the per year calculation of incidence and prevalence is questionable. I am not sure whether such a conclusion can be drawn from data over 6 months and without screening the whole state since there can be lots of undetected cases in the community. Please clarify.</p> <p>24. P9L35 - the above comment holds for the statement that incidence among Sudanese children is higher than other countries.</p> <p>25. P10L9-14 - the discussion should be more explanatory regarding what were the outcomes in those diagnosed > 6 yr.</p> <p>26. The discussion section mainly constitute the repetition of results. Please modify the section in depth with conclusions from the results in comparison to available data. There should be critical assessments of existing deficiencies and measures to circumvent the same which would uplift the quality of discussion.</p> <p>27. Please explore whether malnutrition per se has impacted outcomes and survival.</p> <p>Limitations</p> <p>28. There are significant limitations for the study. Institutions based study may not reflect the true burden in society or state.</p> <p>29. The quality of work up seems a significant limitation since the etiological characterization would be blurred.</p>
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	<p>30. Being an epidemiological study, at least one-year data collection rather than 6 months period would improve the credibility of the study.</p> <p>Conclusion</p> <p>31. The diagnosis of post viral DCM require rephrasing appropriately since it is purely clinical.</p> <p>32. The statement that malnutrition and old age are associated with poor prognosis and mortality is not proven by any sort of analysis. Please have valid statistical proof for the same.</p> <p>33. Overall, the language and style of writing requires significant attention.</p>
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REVIEWER	<p>Reviewer name: Dr. Babar Hasan</p> <p>Institution and Country: AKU, Pediatric and Child Health, Stadium Road, Karachi, 74800, Pakistan</p> <p>Competing interests: None</p>
REVIEW RETURNED	25-Dec-2020

GENERAL COMMENTS	<p>I review with interest this manuscript titled, "Pattern of Pediatric Dilated cardiomyopathy in a sub-Saharan African country". The paper tries to describe the presentation and prognosis of DCMP in an African country. As expected the presentation of the disease is late and the prognosis poorer compared to the data from the west. Though intuitive, data from low resource setting are scares and such papers adds to the body of evidence of cardiovascular diseases as neglected diseases in low resource settings. Every effort, thus, should be made to encourage such write ups to be published.</p> <p>Specifics:</p> <p>Introduction:</p> <p>1) "Dilated cardiomyopathy (DCM) is a rare, but debilitating disease of the heart that can lead to heart failure in both children and adults DCM.....". Please check punctuation and grammar in the manuscript.</p> <p>Methods:</p> <p>1) Page 7, "and that they could withdrew from the study at any stage without affecting the management of their children" Withdrew should be withdraw</p> <p>2) It seems from the description that the study was prospective collection of data over a time period? Is that so?</p> <p>3) More details in methods are needed? How was anthropometric measured? Which z-scores or percentiles were used (WHO)? How was ECHO done and which methods were used to measure function and volumes (Simpson, Bullet etc)? How was the etiology determined i.e genetic testing, viral panels, endomoyocardial biopsies? How was mild, moderate, severe dysfunction classified i.e z-socres, quantitative, qualitative?</p> <p>4) Without proper description of how the etiology of DCMP was determined, inference about it being viral vs genetic vs metabolic vs idiopathic cannot be made. I do understand that a detailed etiological workup may not be possible in a resource limited environment but then this limitation should be mentioned as it is i.e by saying what percentage of children underwent a detailed work up for DCMP. This will give authors a chance to discuss yet another aspect of management in low resource settings i.e lack of proper diagnostics like genetic testing, sophisticated metabolic testing. May be couple of sentences on how much of such testing is available in Sudan and if it is what is the cost.</p>
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	<p>Discussion:</p> <p>1) "The three commonest symptoms were shortness of breath in 96.4%, cough and irritability both in 90.9%. (Table 3). Towbin et al (6) study of the Cardiomyopathy registry showed that 71% present with evidence of heart failure, a study from the KSA (10) showed 74% presented with evidence of heart failure ,and 70% presented with heart failure in study from Turkey (13). So our population presented with a severe spectrum of the disease". I am confused what the authors are trying to highlight here? Shortness of breath is a symptom of heart failure? Severity of heart failure is determined by either Ross or NYHA which will make more sense to use. If the authors are trying to depict that their patients presented with much worse symptoms of heart failure then the bet way of doing this will be to look at their Ross or NYHA functional class and compare it to other studies.</p> <p>2) "Regarding the aetiology of DCM, The two commonest causes were post viral in 49% and idiopathic in 45.5%. Familial cases were 4.5% (Table 4). Towbin et al (6) found that the commonest cause of DCM was idiopathic in 66% , Post viral in 16%, and familial in 5% , so our population is different in that post viral have a bigger share compared to the data from the developed world. We think a good proportion of the post viral DCM in our study is not truly....." without proper diagnostics this para and the inference from it is not valid. Too many tables. Tables 4-7 can be deleted</p>
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VERSION 1 – AUTHOR RESPONSE

Hi,

Thank you for your constructive comments , I will respond to your comments and I have highlighted in yellow for your easy reference.

- Title I have amended the title , the title now is Paediatric Dilated Cardiomyopathy in Khartoum State, Sudan: a prospective study.
- in the abstract and in all the parts of the manuscript I have added the numbers before the percentages-
- I have changed the objective to study the incidence, causes and outcome of DCM among children in Sudan
- I have changed developed words and developing worlds and used high income and low income instead.
- I have added a paragraph about child care services in Sudan.
- I have added the inclusion and exclusion criteria and the case definition of DCM
- I have added a paragraph about ventricular dysfunction groups and fractional shortening (FS)
- In the results section I have added the I numbers before the percentages.
- I have replaced Table 1 with a figure, deleted Table 2 , and added a sentence about the children's growth in Khartoum state.
- I amended table 3 by rounding figures to whole numbers.
- I have deleted Tables 4.5 &7.
- I have added Table 3 , the relationship between age at diagnosis and outcome, Table 4 the relationship between NYHA classes and outcome , table 5 the relationship between ventricular function and the outcome.
- I have amended the discussion and the conclusion.
- I have added a paragraph in discussion about lack of diagnostic investigations.
- I have amended limitations

VERSION 2 – REVIEW

REVIEWER	<p>Reviewer name: Dr. Shine Kumar</p> <p>Institution and Country: Amrita Institute of Medical Sciences and Research Centre, Pediatric Cardiology, Kerala, India</p> <p>Competing interests: None</p>
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GENERAL COMMENTS

The authors have revised the manuscript significantly. However requires further fine tuning to consider for publication. Please find the comments below.

Abstract

1. I would suggest an approval by statistician regarding the calculation of prevalence and incidence mentioned in the study.
2. P3L45-47. The statistical evidence that the mentioned factors contribute to mortality is very vague. The statistical analysis in this regard require more refinement and should be well explained.

Methodology

3. There is no mention of statistical methods applied. Kindly include the same.
4. Please mention that diagnosis of post viral myocarditis was purely clinical and no viral studies were done. Similarly the genetic work up was also not done due to nonavailability. These should be mentioned in limitations also.

Results

5. Please use Ross classification for functional class especially in children less than 5 years. NYHA is applicable to older children only.
6. P9L44 – 49. The criteria for classification of severity of lv dysfunction by echo should be mentioned in methods than in results.
7. P9L56 – 58. The etiology is unclear for the siblings who died. Whether it was due to DCM or something else? If not due to DCM then only one family with sibling having DCM may be labelled as familial. Please correct accordingly.
8. P9L60 – It would be better to remove data regarding arrhythmia since there is no conclusive evidence and you have not diagnosed tachycardia induced DCM as a cause.
9. P10L7,8 – Please mention the diagnosis of those presented with acute heart failure requiring inotropic support.
10. There is no detailed description of deaths with respect to diagnosis as pointed out earlier.
11. The statistical significance of mortality related to age and symptoms is very vague. Kindly explain in detail the statistical relevance with appropriate data.
12. Kindly mention whether there were any syndromes associated with DCM

Discussion

13. P11L60 – the statement that DCM in Sudan is associated with failure to thrive is not true. This statement can be only made if one has ruled out all other causes of failure to thrive and only DCM was confirmed as cause for the same. It should be rephrased as majority of DCM patients had failure to thrive which likely is multifactorial and poor nutrition could be a major factor given the socioeconomic issues in the region.
14. P12L48-50 – the statement that viral DCM is clinically diagnosed is to be mentioned in methods.

Limitations

15. Kindly also mention the limitations in Sudan regarding work up of DCM cases with regard to viral and genetic studies.

Conclusion

16. Three factors - older age, malnutrition and severe disease are mentioned as factors associated with poor prognosis. The statistical

	<p>data regarding age and severe disease with mortality is very vaguely presented. The corresponding tables need to be restructured with appropriate p values and should be clearly explained in results. With respect to malnutrition conclusion totally contradicts the statement in results that there is no association with mortality. P10L22-24. Kindly rectify the same.</p> <p>17. The statistical analysis presented for identifying factors associated with mortality are unclear. The analysis needs to be more robust and well explained in results with appropriate depiction in tables 3&4.</p> <p>18. Overall, the language, style of writing and statistical methods with appropriate interpretation requires significant improvement.</p>
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REVIEWER	<p>Reviewer name: Dr. Babar Hasan Institution and Country: AKU, Pediatric and Child Health, Stadium Road, Karachi, 74800, Pakistan Competing interests: None</p>
REVIEW RETURNED	04-Feb-2021

GENERAL COMMENTS	<p>Resubmission review of Pattern of Pediatric DCMP in Africa.</p> <p>I review with interest this manuscript titled, "Pattern of Pediatric Dilated cardiomyopathy in a sub-Saharan African country".</p> <p>Introduction:</p> <p>1) "In Sudan, the parents tend to look for medical care at secondary levels i.e.in hospitals rather than primary care facilities such as health centres, especially if they believe that the child could have a serious illness. Secondary and tertiary care hospitals will accept children who presented to their Accident and Emergency department and the parents understand that this is the fastest way to be seen and admitted if required. Parents from other states in Sudan will tend to bring their children to Khartoum state; they have a perception that the medical services in Khartoum state are of a higher quality than the rest of the country." So the point they are trying to make is that the cases presenting at their hospitals was representative of majority of cases in Sudan and thus they can calculate incidence. If that is the case then they should mention this otherwise this paragraphs seems meaningless. The authors have mentioned this in the study design thus making this paragraph in the introduction unnecessary.</p> <p>2) Don't begin a sentence with a numerical i.e results page 29, line 6, "32 of the children.....". Begin a sentence as Thirty-two of the children. Will suggest rectifying this everywhere in the manuscript.</p> <p>3) So mean duration of follow up is only mentioned on 27 children only. Why isn't this mean calculated on all 55?</p> <p>4) Results page 29, line 21: unsure what this statement is adding. Why not just mention the most common age group at diagnosis.</p> <p>5) Rewrite the whole line 21-28 on page 29. It has too many redundancy. There is also no need for figure 1</p> <p>6) Page 30 line 4, is furosemide.</p> <p>7) Page 29 line 59: "There were another two children....." should be written In the other 2 children.....</p> <p>8) Page 30 line 12: 36 deaths (65.51%), round off all decimal places to single decimal place.</p> <p>9) Discussion: Page 30 line 34-40 is a repetition and should be removed.</p> <p>10) Page 49 line 60 "his" should be 'this'.</p> <p>11) There is no need for table 2</p> <p>12) Some of the stats need to be redone. Comparison of NYHA III vs IV doesn't make sense. I will recommend Group 1 (NYHA1 and II) vs Group 2 (III and IV). Also categorize the age based on a median cut off into late and early presenter. Similarly the analysis for</p>
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	growth impairment and its effect on mortality should be also done with those with <5% vs those who have normal weight.
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VERSION 2 – AUTHOR RESPONSE

Dear Editor in chief and Reviewers
Thank you for your valuable comments
Please find my responses

regards

Reviewer 1

- 1- I have removed the paragraph
- 2- I have amended accordingly and changed the numerical values in the beginning of the sentences to words rather than digits
- 3- I have calculated the follow up duration for the 27 children who were known to have DCM and under follow up , the other 28 children were newly diagnosed and they were not followed up
- 4 &5- I have amended the paragraph and made it shorter , I have kept Figure 1 as it illustrate that there was no big difference between the age and the age of diagnosis indicating short follow up and poor survival.
- 6- I have amended the spelling mistake
- 7- I have deleted this sentence as suggested by the second reviewer
- 8- I have rounded up the decimal space
- 9- I have deleted the repeated sentence.
- 10- I have corrected the typing mistake
- 11- I have kept Table 2 to give an idea about the treatment received.
- 12- I have removed all the statistical analysis as suggested by the editor

Reviewer 2

- 1,2 and 3- I have removed all the statistical analysis as suggested by the editor
- 4- I have added that post viral diagnosis was a clinical diagnosis and the advanced metabolic, genetic and viral studies are not available in the country .I have added this to limitation section as well
- 5- I have amended accordingly
- 6- I have moved the criteria for LV dysfunction to the method section
- 7- I have amended accordingly , the deaths were related to DCM.
- 8- I have amended that and deleted the data regarding arrhythmia.
- 9&10- I have added that there was no difference in mortality according to aetiology
- 11- I have removed all the statistical analysis as suggested by the editor
- 12- in the 55 children with DCM there was no syndrome
- 13- There was statistically significant difference when comparing the rate of failure to thrive in children with DCM to the rate of failure to thrive in the children of Khartoum state
- 14- I have added that the diagnosis of post viral DCM is clinical to the method and limitation
- 15- I have added the non availability of genetic, viral and metabolic testing to the limitation section.
- 16,17,18- I have removed the statistical analysis and made some changes o the conclusion.

Editor in chief

- 1- I have deleted the statistical analysis
- 2- I have moved the incidence and prevalence of DCM to the result section and stated that it is an approximate figure
- 3- I have deleted lines 14-26 in page 10
- 4- I have deleted Tables 4 and 5 , and amended Table 3 by deleting the statistical analysis
- 5- I have rounded up % to whole numbers
- 6- I have shorten the discussion
- 7- I have amended the conclusion

VERSION 3 – REVIEW

REVIEWER	Reviewer name: Dr. Babar Hasan
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	Institution and Country: AKU, Pediatric and Child Health, Stadium Road, Karachi, 74800, Pakistan Competing interests: None
REVIEW RETURNED	13-Mar-2021

GENERAL COMMENTS	<p>I review with interest this manuscript titled, "Pattern of Pediatric Dilated cardiomyopathy in a sub-Saharan African country".</p> <p>Introduction</p> <ul style="list-style-type: none"> - Page 5 line 12-14: "Normal LV wall thickness" this may not always be the case. I will just remove this statement. - Page 5 line 21, Technically heart transplant is a treatment and not a complication of DCM. I will remove that from the list of complications as it is out of place there. - Page 5, line 31 " With older age" should be "Older age" remove with <p>Results:</p> <ul style="list-style-type: none"> - Page 9, line 27-30. Round off all the continuous data (mean years) to one decimal place. Also the statement can be written as 7.5 ± 5.4 years and similarly for age at diagnosis. - Page 9 line 35, why is follow up duration only mentioned for 27 children and not the whole cohort? <p>Discussion:</p> <p>Needs language, grammar and use of paragraphs editing which can be done at the proof reading point. These changes are needed for the discussion to flow better.</p> <p>Conclusion</p> <p>Page 14, line 27-29: Rephrase to "The mortality rate is also high as compared to pediatric DCM patients in high income countries"</p> <p>Page 14, line 31: Improvement in health system as a whole is needed.....</p> <ul style="list-style-type: none"> - I am still not clear what figure 1 is adding. It can be removed as it is confusing.
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REVIEWER	Reviewer name: Dr. Shine Kumar Institution and Country: Amrita Institute of Medical Sciences and Research Centre, Pediatric Cardiology, Kerala, India Competing interests: None
REVIEW RETURNED	13-Mar-2021

GENERAL COMMENTS	<p>Dear authors</p> <p>The authors have well addressed the revisions. I would suggest the following minor revisions.</p> <ol style="list-style-type: none"> 1. The last two sentences in introduction reflect the conclusion from the article (P5L44-49). Kindly include those in discussion rather than in introduction. 2. P9L27. It is better to rephrase the line as "The age of the children ranged" rather than "The children ages". 3. P9L36. While mentioning mean duration as 1.2 years please add standard deviation value. 4. P10L25. Please change s of spironolactone to capital case. 5. In able 1 it would be appropriate to mention as "shortness of
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	breath" rather than "breathing". 6. In table 3 please add percentage to all numerical values.
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VERSION 3 – AUTHOR RESPONSE

Dear Editor in chief and Reviewers
Thank you for your valuable comments
Please find my responses

Reviewer 1

- 1- I have moved these sentences from the introduction to the discussion
- 2- I have amended the suggested change
- 3- I have added the standard deviation
- 4- I have corrected the typing mistake
- 5- I have amended table 1
- 6- I have amended table 3

Reviewer 2

- 1- I have deleted the statement
- 2- I have removed heart transplant from the list of the complications
- 3- I have amended the suggested changes
- 4- I have amended the suggested changes
- 5- The follow up duration is for the 27 children who were already known to have DCM and under follow up, the other 28 children were newly diagnosed and had no prior follow up
- 6- I have amended the changes
- 7- I have rephrased the suggested sentence
- 8- I have amended the sentence
- 9- Figure 1 illustrates that there was no big difference between the age and the age of diagnosis indicating short follow up and poor survival.

VERSION 4 – REVIEW

REVIEWER	Reviewer name: Dr. Shine Kumar Institution and Country: Amrita Institute of Medical Sciences and Research Centre, Pediatric Cardiology, Kerala, India Competing interests: None
REVIEW RETURNED	25-Mar-2021

GENERAL COMMENTS	Dear author, The revisions done are appropriate. The manuscript is accepted.
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REVIEWER	Reviewer name: Dr. Babar Hasan Institution and Country: AKU, Pediatric and Child Health, Stadium Road, Karachi, 74800, Pakistan Competing interests: None
REVIEW RETURNED	31-Mar-2021

GENERAL COMMENTS	Please remove figure 1. It is confusing and not adding much. Please publish this paper after removing figure 1
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VERSION 4 – AUTHOR RESPONSE