## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Anthracycline induced Cardiotoxicity: Prospective Cohort Study from Pakistan. |
| **AUTHORS** | Shaikh, Abdul Sattar; Saleem, Ali; Mohsin, Shazia; Alam, Muhmmad; Atiq, Mehnaz |

## VERSION 1 - REVIEW

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| **REVIEWER** | Jean-Jacques Monsuez<br>Cardiology<br>Hôpital René Muret, Hôpitaux Universitaires de Paris Seine Saint Denis, France |
| **REVIEW RETURNED** | 22-Aug-2013 |

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| **GENERAL COMMENTS** | In this manuscript, AS Shaik et al provide valuable data on the cardiac prognosis of children reveiving anthracyclines, mainly doxorubicin, daunorubicin (or combination of both) for malignant diseases, mainly ALL (70/110). The study should be regarded with interest for 3 main reasons:<br>1 Follow up of children provides data on incident cardiac complications overtime, at 1 month and 1 year, respectively (15 and 28 children with cardiac dysfunction, respectively). Early cardiac toxicity (14% at 30 days) is relatively high and should be underlined by the authors, using an additional reference, e.g. Circulation 2005, 112: 3754, or a review , e.g., their ref 3. They should add a comment of this issue in the Discussion section.<br>2 Onset of diastolic and systolic dysfunctions are well depicted, with an approach also much more detailed than in many other publications. One interesting finding of the study is that children develop either diastolic or systolic dysfunction, or their combination, but not their succession overtime. By contrast, previous studies showed that diastolic dysfunction is an early marker of increased risk for subsequent systolic dysfunction (Lee et al, Stoddart, JACC 1992, 20: 62).<br>3 Most available studies on anthracyclin-related cardiac toxicity were published in Western countries. As data from very different areas such as Pakistan are lacking, the study may also be regarded with interest.<br>The manuscript is well built, with careful treatment of collected data, appropriate statistical analysis and subsequent discussion. It's also easy to read and to understand, with tables in appropriate numbers and relevant data displayed.<br>The manuscript may be improved with minor changes<br>1 cumulative doses of anthracyclines should be expressed in mg/m2,<br>2 the authors should underline that cardiac toxicity is of increased concern today, with regard to the recent withdrawal of desrazoxane. They should add that they did'nt administered this drug to the children. |

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| | 3 Minor spelling/grammatical errors, easy to review at the Editorial office<br>4 Introduction, ln 150, change systolic decomposition for systolic impairment. |

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| **REVIEWER** | Dr. Janez Jazbec, MD, PhD<br>University Medical Center Ljubljana<br>Children's Hospital<br>Dept. of Hemato-oncology |
| **REVIEW RETURNED** | 25-Aug-2013 |

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| **GENERAL COMMENTS** | Shakih et. al. Present the results of their prospective study of cardiotoxicity of anthraciclyne therapy in pediatric cancer patinets. Although the results are in consitence with the results of previously published studies on the subject, the context of the study is put in the mileau of developing country. The study design , methodes used and the stat analysis are adequate as well as the interpretation of the results. The major weaknes of the study is significant drop-out of the patiens which should be better addressed. |

**VERSION 1 – AUTHOR RESPONSE**

| **Reviewer: Jean-Jacques Monsuez**<br>**Cardiology**<br>**Hôpital René Muret, Hôpitaux Universitaires de Paris Seine Saint Denis, France** | |
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| 1) Follow up of children provides data on incident cardiac complications overtime, at 1 month and 1 year, respectively (15 and 28 children with cardiac dysfunction, respectively). Early cardiac toxicity (14% at 30 days) is relatively high and should be underlined by the authors, using an additional reference, e.g. Circulation 2005, 112: 3754, or a review, e.g., their ref 3. They should add a comment of this issue in the Discussion section | We agree with the reviewers, and an additional reference along with comments has been incorporated in lines 284-86. |
| 2) Onset of diastolic and systolic dysfunctions is well depicted, with an approach also much more detailed than in many other publications. One interesting finding of the study is that children develop either diastolic or systolic dysfunction, or their combination, but not their succession overtime. By contrast, previous studies showed that diastolic dysfunction is an early marker of increased risk for subsequent systolic dysfunction (Lee et al, Stoddart, JACC 1992, 20: 62). | We also observed same pattern in our study population, at acute stage most of the children had isolated diastolic dysfunction and in these children systolic dysfunction develop later on. We also observed new cases develop dysfunction with progression of time.<br>Comments have been incorporated in lines # 308-13. |
| 3) Most available studies on anthracyclin-related cardiac toxicity were published in Western countries. As data from very different areas such as Pakistan are lacking, the study may also be regarded with interest. | Yes we agree, studies from our country is lacking. |
| **Comments** | |
| **1)** cumulative doses of anthracyclines should be expressed in mg/m2 | Correction done as mg/m$^2$ in lines # 92, 238, 263, 324, table 1 and 4 |
| **2)** The authors should underline that cardiac toxicity is of increased concern, with regard to the recent withdrawal of desrazoxane. They should add that they did'nt administered this drug to the children. | Mentioned in line # 180-81, 351 |
| **3)** Minor spelling/grammatical errors, easy to review at the Editorial office | We also tried to correct them |

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| **4)** Introduction, ln 150, change systolic decomposition for systolic impairment. | Change done Line # 153 |
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| **Reviewer: Dr. Janez Jazbec, MD, PhD**<br>**University Medical Center Ljubljana, Children's Hospital**<br>**Dept. of Hemato-oncology Bohoričeva 20 1000 Ljubljana** | |
| Shakih et. al., Present the results of their prospective study of cardiotoxicity of anthraciclyne therapy in pediatric cancer patients. Although the results are in consistence with the results of previously published studies on the subject, the context of the study is put in the mileau of developing country. The study design, methods used and the stat analysis are adequate as well as the interpretation of the results.<br>**The major weakness of the study is significant drop-out of the patients which should be better addressed.** | Treatment and follow up compliance always remain major issues in our country due to multiple factors.<br>Addressed in flow diagram and in lines # 341-51. |
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| **Additional changes done** | In line #<br>74 (Pakistan written in place of developing countries)<br>94- 95 (typo error in results corrected)<br>101-102 ( conclusion modified)<br>165 (typo error corrected) |

**VERSION 2 – REVIEW**

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| **REVIEWER** | MONSUEZ Jean-Jacques<br>Hôpital René Muret, France |
| **REVIEW RETURNED** | 18-Sep-2013 |

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| **GENERAL COMMENTS** | All comments suggested to the authors were appropriately taken into account in the revised submission.<br>2 minors changes more:<br>- ln 285, change " a little high" for "higher than" ( in other studies,mainly from Western countries)<br>- Tbale 1, ln 485: mg/m² also in cumulative dose, column 1<br>Many grammatical errors throughout the Msc should be edited to improve style. |

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: Jean-Jacques Monsuez
Institution and Country Hôpital René Muret, France
1) ln 285, change " a little high" for "higher than" ( in other studies, mainly from Western countries) Corrected.
2) Table 1, ln 485: mg/m² also in cumulative dose, column 1 Corrected.
3) Grammatical errors throughout the Msc should be edited to improve style Grammatical corrections have been made.