Author’s response to reviews


Authors:
Shihai Yang (shihaiyang1@yeah.net)
Linlin Wen (Linlinwen2@yeah.net)
Shuguang Tao (ShuguangTao3@yeah.net)
Jiangrong Gu (JiangrongGu@yeah.net)
Jiangang Han (JiangangHan@yeah.net)
Junping Yao (JunpingYao@yeah.net)
Jianming Wang (jianmingwang@foxmailvip.com)

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Author’s response to reviews:

RE: # BCAR-D-18-00369


Mostafa Mokhles,
Associate Editor
BMC Cardiovascular Disorders

Dear Professor Mostafa Mokhles,

Thank you for sending us the reviewer’s commentary. We have carefully revised our manuscript according to the reviewers’ comments, and the results of new suggested analyses were added in the revised manuscript. In addition, the point-to-point replies and explanations for all reviewers
were included. Finally, we would like to express our sincerely thankfulness to the editor and the anonymous reviewers. We will be grateful for the publication of our work in BMC Cardiovascular Disorders.

We look forward to hearing from you.

Yours sincerely,

Jianming Wang

Department of cardiac surgery,
Children’s hospital in Hebei province,
133 Jianhua Nan Avenue, Shijiazhuang,
Hebei province 050200, China

Email: jianmingwang@foxmailvip.com

Tel: 0311-85911077

Fax: 0311-85911077

Technical Comments:

During the initial technical check, we noticed that you selected the article type (Database), but your manuscript is not formatted accordingly.

Reply to the technical comment

I apologize for our unintended confusion. Since the study is a NIS database-based research study, we first selected the article type as database and used the format of research article. Thus, we have re-selected the article type as research article in the revised manuscript to comply with the journal rules and avoid confusion.

Point-to-point response to reviewers' comments.
Jamie Romeo (Reviewer #1): Overall comments

It seems that you potentially have nice data which could merit some nice and useful results. However, in my opinion some crucial details, variables and analyses are missing to create clinical value and answer currently important questions in the discussion about TOF repair. The data and the statistical analyses are too limited to substantiate the conclusions or suggestions made in the manuscript.

Reviewer #1: Specific comments Comment (1)

Page 7. Lines 17-20: Age at the surgery was calculated by the summing of the age at admission and the number of days from admission to the surgery. You subsequently had to eliminate 153 of 1,112 (13.8%!) of the patients because the number of days from admission to surgery was not available. First: does the database not register dates/birthdates, admission dates and surgery dates? Second: if not, even if the number of days between admission to surgery is unavailable, how much can this be? This is usually 1, maximally 2 days. What are the changes that it would cause a patient to shift to another group? How many of the 153 were at 'borderline age' so near the age-group boundary?

Reply to comment (1)

The authors would like to thank the reviewer for the valuable suggestions. In order to address the reviewer’s concern, we re-included the 153 patients with missing data on days from admission to surgery. The age of repair in these patients were imputed with the mean number of days from admission to surgery of the study population. All tables were reanalyzed and revised to the Results and Tables in the revised manuscript. Consistent to previous results of excluding these patients, we found that children > 30 days old at the time of repair had a significantly shorter length of hospital stay than those aged ≤ 30 days (31-90 days old: -12.5 days, 91-180 days old: -18.4 days, and >180 days old: -18.6 days) after adjustment for insurance status, admission type, heart catheterization and gastrostomy tube insertion in the multivariate analysis (Table 3). When treated as continuous variable, older age at repair was also significantly associated with slightly shorter length of hospital stay (β: -0.02). As well as association between age at complete repair of TOF and length of hospital stay, multivariate analysis showed that the risk of postoperative complications was about 40% lower in children of 91-180 days old and >180 days old compared to children ≤ 30 days old (aOR: 91-180 days old = 0.60 and > 180 days old = 0.60) (Table 3). When treated as continuous variable, patients with older age at repair had lower risk of postoperative complications.
In the subgroup analysis of patients with elective (non-emergent) admissions, older age was associated with a shorter length of hospital stay as compared to those ≤ 30 days old at repair (31-90 days old: -2.94 days, 91-180 days old: -3.95 days, and > 180 days old: -4.29 days) in the multivariate analysis; however, the difference was not significant in the group 31-90 days old. Multivariate analysis indicated that older age groups had a 42% to 57% lower odds of postoperative complications compared to infants ≤ 30 day old at repair (adjusted OR [aOR]: 31-90 days old = 0.43, 91-180 days old = 0.58, and >180 days old = 0.58); however, the difference was not significant among the groups (Table 4).

Comment (2)

Especially interesting is the subgroup analysis focusing on elective correction. In the methods section: elective correction is defined as non-emergent. However, you also mention in the discussion (page 11, line 46-49) you do not distinguish between cyanotic and asymptomatic disease. Who are the patients who undergo emergent surgery? What is the definition of emergent surgery and what is the distribution of cyanotic patients in both the emergent group and the elective group? I would assume that non-emergent would also be non-cyanotic? Furthermore, then the question whether prior palliation has been used is also clinically important, because these are different patients.

Reply to comment (2)

The authors would like to thank reviewer for the valuable suggestion. No direct data of whether a patient is cyanotic or non-cyanotic (asymptomatic) is available in the dataset. However, we assumed that those underwent emergent surgery would be cyanotic whereas those underwent elective surgery (non-emergent) would be non-cyanotic. In addition, we re-checked the database and extracted information about palliative shunt (systemic to pulmonary artery shunt, ICD-9: 39.0) (Table 1). However, the patient number who underwent shunt palliation were really small (Table 1). Thus, we’ve left them out of the analyses in present study.

Comment (3)

You decided to categorize age. Have you tried entering age in days as a numerical, continuous variable into you regression analyses?

Reply to comment (3)
The authors would like to thank reviewer for the valuable suggestion. In order to address the reviewer’s concern, we added age as a continuous variable into models (Table 3 and 4). The analyses have been re-performed, which have been revised to the Results and Tables in the revised manuscript. When treated as continuous variable, older age at repair was also significantly associated with slightly shorter length of hospital stay ($\beta: -0.02$). In addition, patients with older age at repair had lower risk of postoperative complications after adjustment for insurance status, admission type, heart catheterization and gastrostomy tube insertion in the multivariate analysis. However, in the subgroup analysis of patients with elective (non-emergent) admissions, older age was not significantly associated with length of hospital stay or postoperative complication after adjustment for insurance status, gastrostomy tube insertion and bed size of hospital. Taken together, we suggest that association between age at complete repair of TOF and postoperative complication and length of hospital stay for children may be only existed in early age receiving repair of TOF.

Comment (4)
Length of stay is unlikely to follow a normal distribution. Have you tried a non-parametric approach by comparing medians?

Reply to comment (4)
The authors would like to thank reviewer for the valuable suggestion. The results are generalized from sample to population given the NIS database’s sample design. So parametric approach is adopted.

Comment (5)
The surgical approach towards patients with pulmonary atresia/VSD is fundamentally different. The number of patients with PA is really small. Have you considered leaving them out of the analyses?

Reply to comment (5)
We agree with the reviewer’s concern. The patients with pulmonary atresia have been left out of the new analyses.
Jolanda Kluin (Reviewer #2): Overall comments

This is an interesting analysis on the impact of timing in Fallot patients. The study is executed very well and clearly written. I only have some small comments:

Reviewer #2: Specific comments Comment (1)

Background, line 5: conoventricular instead of conoventruicular.

Reply to comment (1)

We agree with the reviewer’s concern. The “conoventruicular” has been replaced to “conoventricular” in the Background (page 3, line 5) of revised manuscript.

Comment (2)

Background, line 11; lots instead of lost

Reply to comment (2)

We agree with the reviewer’s concern. The “lost” has been replaced to “lots” in the Background (page 3, line 11) of revised manuscript.

Comment (3)

Conclusion. I would recommend to change the sentence on morbidities (In those undergoing elective repair...) in the sentence used in the abstract (In the subgroup that underwent elective repair...)

Reply to comment (3)

We agree with the reviewer’s concern. A shorter paragraph stating “In addition, children > 30 days old at the time of repair had a significantly shorter length of hospital stay than those aged ≤ 30 days. In the subgroup with elective repair, older age was associated with a shorter length of
hospital stay as compared to those ≤ 30 days old at repair, while association between age at complete repair of TOF and postoperative complication was not significant among the groups after adjusting for confounders.” has been corrected to the Abstract in the revised manuscript (page 2, line 11~15). A sentence stating “In the subgroup with elective repair, older age was associated with a shorter length of hospital stay as compared to those ≤ 30 days old at repair, while association between age at complete repair of TOF and postoperative complication was not significant among the groups.” has been corrected to the Conclusions in the revised manuscript (page 11, line 13~16).

Robert M R Tulloh (Reviewer #3): Overall comments

The authors have analysed the NIS database and determined the evidence of risk of complications for Fallot repair at different ages. They conclude that the risk of repair at <30 is higher than at other ages

Reviewer #3: Specific comments Comment (1)

This is an interesting paper analysing the NIS database. As with all retrospective studies, it suffers from the problems of incomplete information about the patients concerned. Permission has to be granted to study this database and this permission needs to be identified in the manuscript.

Reply to comment (1)

The authors would like to thank reviewer for the valuable suggestion. A sentence stating “The present study obtained the certificate number, HCUP-29L23FXS6, and conforms to the data-use agreement for the NIS from the HCUP Project.” has been added to the Methods in the revised manuscript (page 5, line 2~4).

Comment (2)

Abstract. The data suggests that the risk of complications in <30 day infants undergoing repair of Fallot is greater than for children who are older. This information is not new, as the authors themselves confirm in the discussion. Can they reassure us, that it is not just the more severe cases that are operated earlier?
Reply to comment (2)

The authors would like to thank reviewer for the valuable suggestion. In present study, although no direct data of severity is available in the dataset, efforts were made to address this problem. The database provides information on whether the surgery is emergent or elective. We thus assumed those who underwent emergent repair were cyanotic while those underwent elective repair (non-emergent) were non-cyanotic. This factor was considered and adjusted in our analyses (Table 3). In further analysis (Table 4), we tried to eliminate symptomatic patients by excluding the cases of emergent surgical attention, thus to assure that the issue of optimal timing is centered.

Comment (3)

There is no information on the type of operation that these children have had. "Repair" might mean different things to different people, for example transanular patch without VSD closure, might be listed as repair. Can the authors be sure what operation these children have had?

Reply to comment (3)

We agree with the reviewer’s concern. Although this detailed information is not available in the dataset. However, total repair of tetralogy of Fallot was defined that it has been performed one-stage total correction of tetralogy of Fallot with several factors, including patch graft of outflow tract, commissurotomy of pulmonary valve, infundibulectomy, outflow tract prosthesis, prosthetic tube for pulmonary artery, repair of ventricular septal defect, and take-down of previous systemic-pulmonary artery anastomosis. Thus, we considered that the type of operation may be consistent in these children receiving repair of TOF. In order to address the reviewer’s concern, the “surgical types” has been added to the limitation in the revised manuscript (page 10, line 23).

Comment (4)

Results. The length of stay might be for non-cardiac reasons, for example establishing feeding, especially in those with 22q11.2 deletion or cleft palate. Can the authors let us know what it was that kept them in hospital?

Reply to comment (4)
We agree with the reviewer’s concern. Although the detailed information is not available in the dataset. However, the present study showed that chromosomal anomalies included 22q11.2 deletion (DiGeorge syndrome) was not significantly associated with postoperative complication and length of hospital stay among children receiving repair of TOF (Table 3). In addition, association between age at complete repair of TOF and postoperative complication and length of hospital stay was still significant among the groups after adjusting for chromosomal anomalies. Consequently, the effect of 22q11.2 deletion for length of hospital stay has been excluded, while effect of establishing feeding and cleft palate for length of hospital stay was not excluded. In order to address the reviewer’s concern, the “establishing feeding and cleft palate” has been added to the limitation in the revised manuscript (page 10, line 24).

Comment (5)

If the repair was completed at an earlier age, is it possible that they avoided having BT shunt insertion or RVOT stent? Has this been factored into the outcome for these patients?

Reply to comment (5)

The authors would like to thank reviewer for the valuable suggestion. We’ve re-checked the database and extracted information about palliative shunt (systemic to pulmonary artery shunt, ICD-9: 39.0). The patient number who underwent shunt palliation were really small (Table 1). Thus, we’ve left them out of new analyses.

Comment (6)

The funding needs to be described for this study. Unless the authors undertook this in all their own time, someone was paying their salaries and support costs.

Reply to comment (6)

We agree with the reviewer’s concern. A sentence stating “Funding statement: Not funded.” has been added to the revised manuscript (page 12, line 13~14).