Author’s response to reviews

Title: Left ventricular dysfunction postsurgical patent ductus arteriosus ligation in children: predictor factors analysis

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Left ventricular dysfunction post surgical patent ductus arteriosus ligation in children: predictor factors analysis

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Dear Editor, dear Reviewers,

Thank you for reviewing our manuscript entitled "Left ventricular dysfunction postsurgical patent ductus arteriosus ligation in children: predictor factors analysis" and for the opportunity to revise the manuscript.

Please find below our responses and changes according to your comments. Attached you find an unmarked and a marked version (using track changes) of the manuscript.

Thank you for considering our manuscript.
Reviewer #1:

The accompanying manuscript by Bary et al studies the factors that can predict LV dysfunction following PDA ligation. The so-called post-ligation syndrome is a complex phenomenon of significant clinical relevance, and hence studying it is a relevant exercise.

1.

a. Firstly, Table 1 and 2 essentially have the same data for the immediate and 1-month post-ligation variables. These can be combined in one Table.

### thanks a lot, I agree with you. tables 1 and 2 contain the same data so they were merged into one table.

b. More importantly, although statistically significant, the differences (especially in EF and FS) are clinically irrelevant. The authors variably describe these differences as marked, remarkable and significant. I disagree. 58 and 60% EF are clinically indistinguishable.

### Dear sir, we found that 58 and 60% EF are significant by paired t test. Kindly, we put a copy from the statistics here:

**Paired Samples Statistics**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>N</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejectpost1d</td>
<td>58.1800</td>
<td>50</td>
<td>3.46816</td>
<td>.49047</td>
</tr>
<tr>
<td>Ejectpost1m</td>
<td>60.7800</td>
<td>50</td>
<td>2.95745</td>
<td>.41825</td>
</tr>
</tbody>
</table>

**Paired Samples Correlations**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Correlation</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejectpost1d &amp; ejectpos1m</td>
<td>50</td>
<td>.901</td>
<td>.000</td>
</tr>
</tbody>
</table>

**Paired Differences**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejectpost1d –Ejectpost 1m</td>
<td>-2.60000-</td>
<td>1.51186</td>
</tr>
<tr>
<td>-3.02967-</td>
<td>-2.17033-</td>
<td>-12.160-</td>
</tr>
</tbody>
</table>

c. Also, it is not clear if each echo was re-read by the same reader or if they used historical reading data. The inter-observer variability and subjectivity in EF measurements further make this comparison moot.

### Each echocardiography was done by two independent operators, to exclude the interobserver variability. This sentence we added it to the manuscript in the methods / echocardiography.
2. Their data in Tables 3 and 4 and Figures 1 and 2 are unclear and potentially described in an unclear pattern.

a. It appears that Table 3 simply shows univariate correlation. Did they do any multiple regression analysis with age and size, etc. as cofounding factors?

### Table 3 shows a negative correlation between the PDA size and parameters change from pre to early post closure.

b. Similarly, Table 4 compares variables in those with and without EF<29%, again univariate comparison between the groups. They should perform a multiple logistic regression with all these variables and identify if there are any predictors.

### Table 4, group I cases (FS ≤ 29%) early post closure have higher age, wider PDA, lower pre-operative FS% and higher ratio of recurrent chest infections.

c. More importantly, if I understand Table 3 and Figures 1 and 2 correctly, larger PDA would imply that there is a smaller reduction in FS and LVEDd post-op. In other words, FS stays same if PDA is larger. Their discussion implies the exact opposite. Can the authors clarify?

### We found a negative correlation between PDA size and the mentioned parameters.

3.

The authors need to clarify their cohort better –

a. Did this analysis include all PDAs done in the time-period of the study?

### Yes sir, the study included all PDA cases surgically ligated between June 2015 and June 2018.

b. How many patients had echos at all time points indicated in Tables 1 and 2?

### Echocardiography was done for all cases, because we didn't report any mortality in this study. Also, all cases were keen to come for follow up.

c. What is their indication and preferred time for PDA closure - a median age of 15 months seems pretty delayed for PDA closure?

### These patients were referred for surgical closure from pediatricians late; because they presented late in these rural areas of Upper Egypt. The indication for surgical ligation at our center, was cases who had clinical as well as echocardiographic proof of hemodynamically critical isolated PDA.
Reviewer #3:

- It is not clear the unit of measure of FS and LVED changes in the figures.

### Thanks a lot for your comment, we added the units of measure in the figures: PDA size (mm), FS (%) and LVED (mm).

- Is not clear which is the group of patients who received anti failure drugs post op.

### The anti-failure medications were given to nine cases in group I (PDA size >5 mm and FS ≤ 29%).

- Is good to have a statistical analysis on your case series but I am not sure it is power enough.

### Dear sir, we revised the statistics and found it's enough and suitable for this study.

Reviewer #4:

Title:

Page 1 Line 3 We suggest you follow the STROBE guideline for observational studies (cohort study) also when writing the title. This guideline is very good guidance also in the other sections of the manuscript.

### Dear sir, thanks a lot. We have revised the STROBE guideline for this study. That helped us a lot in the revision of this work.

P1 L3 Postsurgical. We think that is one and not two word. Please make sure that it is spelled correctly.

### Thanks a lot, we have changed it into one word "postsurgical".

Abstract:

P 2 L 9 We do not understand what you mean by "viewed as a standout".
Dear sir, standout means noticeable, observable or prominent.

P 2 L 22 Methods: We suggest that all results - also on PDA diameter - are put in the results section and not in methods. Also later you describe data not only preoperatively but also postoperatively and 1 and 6 months later. This should be included also in the abstract.

Dear sir, we made these changes. We put the PDA diameter in the results and the postoperative follow up in the methods.

Background:

P4 L 2 Possible rewrite the first sentence "is a fetal circulation shunt" to "is a shunt in the fetal circulation".

We changed it to "is a shunt in the fetal circulation". Thanks a lot.

P4 L 6 Would authors please explain "happens by unexpected contraction of the PDA wall"?

Thanks a lot, we found the description of these changes in the literature about the neurohormonal and oxygen tension changes that affect the PDA smooth muscles. However, we rewrote the background and removed this sentence.

P4 L11 Authors give numbers on the prevalence of PDA in very low birth weight neonates. It however, it is important to remember that PDA is most prevalent in preterm neonates, and that a large percentage of preterm neonates are born with a low gestational weight (for gestational age). Sometimes weight is used as a proxy for gestational age, if it is not known for certain.

PDA in the very preterm neonate is associated with adverse outcome. The discussion on the management of PDA in preterm neonates is however rather controversial. A very high percentage will close spontaneously. And there is a lack of evidence to demonstrate any benefits from PDA closure. This figure is from Semberova et al. Pediatrics, 2016:140: e20164258.

These patients were referred for surgical closure from pediatricians late; because they presented late in these rural areas of Upper Egypt.

Thanks again for these valuable data. We have revised this reference; we found it valuable for our study.
P4 The "background" would benefit from a re-write in order to be more clear. Present the PDA, why should it be closed, what is the problems in the closure (the postligation cardiac syndrome) and then that it is important to identify preoperative factors that could help to children that are likely to develop postligation cardiac syndrome. Also emphasize that you have studied children and not preterm neonates.

### Dear sir, thanks a lot for these valuable remarks. Already, I made these changes and re-written the background section. I added a data about the postligation syndrome and the preoperative factors that may anticipate it.

P4 L37 Authors state that "This study aims to anticipate the predictor factors of LV dysfunction following PDA surgical ligation". We do however find that identifying associations between pre-operative findings and post-operative LV functions is only a rather small part of this study. We suggest authors including the changes in echocardiographic measures as their primary aim and that a secondary aim is to identify predictor factors of LV dysfunction following PDA surgical ligation.

### Thanks a lot for this point, we changed it to " The current study evaluated the pre and postoperative echocardiographic changes to identify the preoperative predictor factors of LV dysfunction following PDA surgical ligation in children".

P4 L38 "anticipate the predictor factors" We suggest authors consider if they want to "identify predictive factors" or possibly "preoperative factors associated with factors of LV dysfunction following surgical ligation of a PDA".

### thanks a lot, we considered this and changed it, these changes in the previous comment for P4 L 37.

Methods:

Study population

P4 L45 Could authors add information on how the children were selected for this study. Did the cohort include all children operated in the given period of time? Also what is the indication for closure of PDA at this center?

### As we mentioned before, the indication for surgical ligation at our center was cases who had clinical as well as echocardiographic proof of hemodynamically critical isolated PDA. This study included all children operated for PDA ligation during this period.
P 4 L45 Did you exclude children operated for other cardiovascular malformations - you state that they had to be hemodynamically significant? Did you exclude preterm neonates? You may include a flowchart, please look at the STROBE guideline.

### Yes, we excluded these cases "preterm babies; patients with other congenital heart defects; patients with silent PDA and patients with irreversible pulmonary vascular disease". As we mentioned before these cases referred for surgery late.

P 4 L47 Was your follow up complete - Did all the children complete all examinations?

### All cases completed the follow up. They were keen for the check. Also, we didn't report any mortality.

P 5 L55 How did you define "echocardiographic proof of hemodynamically critical PDA"

Does authors have clinical data including blood pressure, need for mechanical ventilation.

### Hemodynamically significant PDA means that: PDA with large shunt volume, \( Qp/Qs > 2 \), LV dilatation, diastolic pressure gradient< 25 mmHg.

All of our cases were hemodynamically stable and all of them were extubated on table. There was no need for mechanical ventilation.

Echocardiography

P 5 L23 Would authors please add information on who performed the echocardiography? Also did you validate the measurements? Did you do any blinding in term of clinical sign/ symptoms indication postoperative PDA ligation syndrome?

### the echocardiography was done by Dr. Mahmoud Nafaie and Dr Heba Qubaisy. Validation through comparison of the data obtained by the two operators.

P 5 L32 Authors write "and listed for the body surface", not sure "listed" is the correct word to use.

### thanks a lot, it should be "indexed to". We changed it.

P 5 Did you perform more than one cardiac cycle - often three consecutive cardiac cycles were acquired and digitally stored for an offline analysis.

### The five cardiac cycles were acquired and digitally stored for analysis.
P5 L36 Could authors please add further information on how the PDA diameter was measured. Was it with or without color Doppler. Was it measured at the most narrow point?

### PDA diameter was measured using color-Doppler in short axis parasternal view and modified high parasternal views, measuring the narrowest point.

Statistics

P5 L 50 In order to evaluate the relationship between PDA size and changes in echocardiographic parameters authors used using the Pearson linear correlation and linear regression analysis. We are concerned that this is not sufficient in this case as you have both repeated measurements and multiple comparisons.

### Dear sir, we did a correlation between the pre-operative measures' changes and the immediate post-operative values; which became defective and not correlation with all the measurement, which may later in many patients became normal like pre-operative measures.

P5 L39 Authors write that "we classified our patients into two gatherings as indicated by FS % based on a definition of LV systolic dysfunction; group I with FS ≤ 29% and group II with FS > 29%.

So was this the preoperative FS or one of the postoperative measurements? We presume it is postoperatively. This information needs to be included in the section on the study population.

In order to be able to work further on this, You need to present descriptive data on the two groups in order to establish if they differed in other ways (that is essentially what you do in Table 4). Here you find several variables that are different between the two groups including PDA diameter. Authors then argue that the differences you find are predictors - that PDA diameter is a predictor of FS postoperatively. However, you need to do further analysis and possible adjust for confounders.

##### Yes sir, it is a post-operative data. As post-operatively, we classified these patients after LV dysfunction; in a trial to find a pre-operative predictor for the post-operative decrease in FS.
Results:

P6 L 3 "The respiratory tract infection and the postoperative hospital stay were recorded" are these the data used in table 4?

### Yes, these data were recorded in table 3 (were merged table 1 & 2, so the table 4 became table 3)

P6 L10 Replace "non-significant changes" with "was unchanged" or "did not change".

### We changed it. Thanks a lot.

P6 L 5 + 13 As explained under Table 1 and 2, Make this into one. Please see below.

### Ok, we combined them into one table.

P6 L 32 If authors want to identify "predictive factors" these factors must happen before the outcome of interest.

### In the current study, we evaluated the pre and postoperative echocardiographic changes to identify the preoperative predictor factors of LV dysfunction following PDA surgical ligation in children.

P6 L 50 "Our clarification for this perception is that the….." the first part of this sentence is not very clear. It could possibly be removed.

### We removed the first part of this sentence. Thanks a lot.

P7 L3 The reason for the cardiovascular instability after PDA ligation is rather complex and remains to be clarified.

Table 1 and 2 both contain data on comparison between the post ligation LV systolic function, dimensions & LA/AO ratio in children after PDA closure. In general should one be able to understand tables and figure from the legends and explanations. So I suggest authors add information on number of children, where the examination took place etc.
However, at both tables contains the same data only in table 1 you compare to preoperative values and in table 2 to first day post ligation. The authors should put the data in one table, as most of the data are listed twice. As already mentioned should authors reconsider the statistics used.

### Ok, we combined them into one table. Also, we added the data about the number of cases. This examination was done in cardiothoracic surgery and pediatrics departments at Qena University Hospital. This is already mentioned in methods of the study.

Table 3 except from data on EF table 3 contains the same data as figure 1 and 2. Possibly the R and p-values could be added to the Figure.

### Table 3 shows a negative correlation between the PDA size and parameters change from pre to early post closure.

Table 4 Please add information on abbreviations and definitions (how was hospital days and Recurrent chest infections).

##### Dear sir, Firstly, I have added information on abbreviations and definitions.

Secondly, about the hospital stay and chest infection: Group I cases (with FS ≤ 29%) had more hospital stays as some of them developed dyspnea and post-operative heart failure; and cases with large PDA size were more in this group. So, they were more susceptible to increased pulmonary flow and chest infection.

Discussion

P6 L 41 Would remove the first three lines. And rather start the discussion with a short overview of our findings.

### Ok, we removed the first three lines with the reference.

P7 L 5 Authors write that Galal et al. (your reference number 14) demonstrated that children with PDA had significant deterioration in FS immediately after PDA closure, which was followed by normalization within six months. They did compare children with PDA > 3.1 mm to children with a PDA < 3.1 mm and found that PDA dimeter was associated with left ventricular
performance after PDA closure (percutaneous or surgical). The children in that study were older compared to your study. Children with small and large PDA have the same SF preoperative but a decline is found in children with a large PDA postoperatively.

P 7 L 28 Mechanisms behind the postligation cardiac syndrome are complex and probably not fully understood. Speculations on PDA ligation being followed by altered coronary artery perfusion have been made.

P 8 Would authors please point out strengths and limitations of their study. One limitation is the lack of a control group. Therefore, although echocardiograms were performed before and after PDA ligation and each patient served as his or her own control, you can't control for the effects of anesthesia or the stress of surgery. Also did any of the children receive inotropes during echocardiographic evaluation?

#### thanks a lot sir, I agree with you that the lack of control group is a limitation for this study. Therefore, although serial echocardiograms were performed before and after surgical PDA ligation and each patient behave as his or her own control, we could not control for the impact of anesthesia or the stress of surgery on cardiac function. Other limitations of our study include the retrospective nature of the study design that might not be the proper method for confirmation of studied relationships and the relatively small number of the studied groups. We added these limitations at the end of the discussion.

Also, children didn't receive any inotropes during echocardiography examination.

P 8 Discuss your choice of SF for evaluation of LV function. SF is a load dependent measure of contractility used to evaluate systolic LV function. Could that be a problem, assuming both pre- and afterload changes after PDA closure?

#### Fractional shortening is among the simplest methods for quantifying LV systolic function. Fractional shortening is the percentage of change in LV cavity dimension with systolic contraction and is expressed by Formula 3.1:

\[
FS = \frac{LVEDD - LVESD}{LVEDD} \times 100\%
\]

LVEDD
Where LVED is the LV end-diastolic dimension and LVES is the LV end-systolic dimension. Fractional shortening is conceptually a one-dimensional measure of ejection fraction. The advantage of fractional shortening over calculated ejection fraction is that the measurements are simply and quickly obtained. In addition, the values are not cubed, so any errors in measurement are not magnified.

P8 L 6 Also, significantly preoperative low values of LVEDds were detected in those with postoperative FS ≤ 29% (group I). Compared to? Is that group 2?

##### preoperative LVEDs of the group showing early postoperative FS ≤ 29% was compared to preoperative LVEDs of the group showing early postoperative FS ≥ 29% and showing significance.

P8 L 14 "Additionally, we found a significantly lower ratio of pre ligation FS in group I and we think that this finding is a reasonable reflection of higher LVEDd in this group according to FS calculation equation." We do not understand this sentence.

##### According to the equation of calculation of fractional shortening by the formula FS equals (LVEDD - LVESD / LVEDD) x 100 as value of LVEDD is small the FS will be higher and vice versa

We suggest authors consider the work by Noori et al The Journal of Pediatrics, June 2007

Noori et al investigated preterm neonates. When adjusted they found that preligation PDA size correlated significantly with changes in LV output at 2 hours postligation. Indicating that the larger the PDA, the greater the reduction in LV output after ligation.

Also Afif F. EL-Khuffash and Patrick McNamara have some interesting points on PDA ligation.

##### Dear sir, these two studies were conducted on preterm babies. As I mentioned before these cases were excluded from our study.