Author's response to reviews

Title: First-attack Pediatric Hypertensive Crises Presenting to the Pediatric Emergency Department

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Author's response to reviews: see over
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Dear Editor-in-Chief,

Enclosed you will find the revised manuscript entitled "First-attack Pediatric Hypertensive Crises presenting to the Pediatric Emergency Department”. In this revised manuscript, we have addressed the reviewers’ concerns and made the mandatory style changes to meet the style of the journal: BMC Pediatrics. We wish to thank you for allowing us to resubmit this revised manuscript and hope that you will now find it acceptable for publication in the BMC Pediatrics. I would very like to make any further revision followed by your comments and it would be highly appreciated if this manuscript could be smoothly run to publication process.

We thank for your assistance in improving our manuscript. Looking forward to hearing from you soon.

Best regards,

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Dear reviewer #1:

Enclosed is our revised manuscript (*First-attack Pediatric Hypertensive Crises presenting to the Pediatric Emergency Department*). We appreciate the constructive comments of your review and have revised the manuscript. Below are our replies to the reviewers:

Itemized comments

**Patient population:**

1. *Exclusion criteria: What is “a medical condition incompatible with the definition of HTN in children and adolescents of 2004” ?*

   Answer: Thanks for your recommendation. The change of definition of pediatric hypertension have been made since 2004. Some patients was diagnosed as hypertension before 2004, but actually presented with BP below the 95th percentile. We excluded those patients.

   On page 6 in line 6:
   
   We excluded the pediatric patients as below: the actual BP below the 95th percentile of BP, the final diagnosis of transient hypertension, asymptomatic hypertensive patients, and incomplete data; including inadequate body height or weight data, and no repeated BP measurement data.

   2. *28 patients with asymptomatic hypertension should NOT be included in the study (as it is an EXCLUSION criterion)*

   Answer: Thanks for your recommendation, and we have corrected the neglect. The 28 asymptomatic patients did have been excluded.

   On page 6 in line 11:
   
   Sixteen patients were excluded for having a BP less than the 95th percentile, 28 were excluded for asymptomatic hypertension, 10 were excluded due to a final diagnosis of transient hypertension, and three were excluded due to inadequate data.

   3. *What does it mean “Severity was based on the primary diagnosis” ?*

   Answer: Thanks for your recommendation. We have corrected the sentence.

   On page 7 in line 1:

   Severity was based on the presence of end organ damage.
4. *Staging of HT (stage 1 and 2) should be mentioned here in the text*

Answer: Thanks for your recommendation. We have corrected the sentence.
(On page 7 in line 2)

**BP measurements:**

5. *ABPM is mention in methods, however, no data on the results of ambulatory blood pressure monitoring are given in the Result section.*

Answer: Thanks for your recommendation. Originally, we designed to F/U BP level by using ABPM, but actually only a few patients had used the device. So we omitted the description of ABPM.

6. *Why SYSTOLIC BP was not taken into account in the definition of hypertensive urgency?*

Answer: According to the definition of hypertensive crisis in adult, the diastolic BP usually greater than 120 mmHg. For the definition of hypertensive crisis in children, there is still a blurred borderline about the critical blood pressure, Dr. Kaplan NM suggested generally more than 180/120mmHg, Dr. Koshy AG suggested the critical BP level for patients is less than 10y/o >160/105mmHg, for those is more than 10 y/o >170/110mmHg. In our study, we used the SBP or DBP more than 99th percentile plus 5 mmHg as the critical threshold. We have made correction to avoid any misunderstanding. So the systolic BP was taken into account in the definition of hypertensive urgency.

On page 9 in line 4:

Hypertensive urgency was defined by us as an elevation in SBP/DBP higher than the 99th percentile plus 5 mmHg with any complication related to the HTN and no evidence of target-organ lesions.

7. *How the end organ damages were specifically defined and detected?*

Answer: End organ damages were defined as impairment renal, myocardial, renal, hepatic, and hematologic, and neurologic manifestation, which all derived from HTN. The abnormal data that patients had never been suffered from before and relieved after BP recovering would be though as acute end organ damages derived from HTN. Abnormal finding including abnormal EKG finding,
elevated renal function, elevated liver function test, and any neurologic manifestations, such as headache, altered consciousness, dizziness. (on page 9 in line 12)

8. Were all the multiple tests to diagnose essential hypertension (to exclude secondary HT) been performed in ALL children during the stay in emergency dpt.?

Answer: Thanks for your recommendation. The surveys performed in PED were those the physician thought as necessary and should be obtained at the first time to check up and to exclude out other emergent problems. The multiples tests were performed during hospitalization or at OPD to exclude secondary HTN. All the data during hospitalization and from OPD were reviewed to exclude the causes of secondary hypertension. Unless the history was clear, the diagnosis of essential hypertension was merely impossible in the PED.

Results:

9. Give exact primary renal and endocrine diagnoses.

Answer: Thanks for your recommendation. The individual diseases were detailed in the revised manuscript. The previous “endocrine” was changed to “endocrine/metabolic” to include those metabolic diseases.

On page 12 in line 12:

The renal disease included nephritic syndrome (n=2, 14.3%), IgA nephropathy (n=2, 14.3%), Post streptococcal glomerulonephritis (n=1, 7.1%), end stage renal disease (ESRD), Henoch-Schönlein purpura with glomerulonephritis (n=1, 7.1%), ureteropelvic junction obstruction (n=1, 7.1%), Alport syndrome with ESRD (n=1, 7.1%), Focal segmental glomerulosclerosis with ESRD (n=1, 7.1%), polycystic kidney (n=1, 7.1%), Alstrom syndrome with chronic renal insufficiency (n=1, 7.1%), inborn error, hyperammoniemia with ESRD (n=1, 7.1%), ESRD s/p renal transplantation (n=1, 7.1%), and SLE with lupus glomerulonephritis (n=1, 7.1%). The endocrine/metabolic disease included hyperthyroidism (n=3, 33.3%), diabetes mellitus (n=3, 33.3%), and hyperaldosteronism (n=1, 11.1%), adrenal hyperplasia (n=1, 11.1%), methyl malonic academia with hyperuricemia (n=1, 11.1%).

10. Give exact numbers of the patients (NOT saying “More than half”)

Answer: Thanks for your recommendation. We have corrected it in our revised manuscript.
On page 13 in line 3:
A total of 33 (60%) patients visiting to the ED were hospitalized: 24 to wards, 7 to the pediatric intensive care unit (PICU), and 2 to the pediatric observation unit (POU) of the ED.

11. Give exact numbers of the patients (NOT saying “A positive family history was present only in older patients”)

Answer: Thanks for your recommendation. We have corrected it in our revised manuscript.

(On page 13 in line 8)

12. The authors say that “Clinical manifestations and severity had a correlation with age” but all but one characteristics did NOT correlate with age acc. the p-values in the Table 1.

Answer: Thanks for your recommendation. In our revised manuscript, we have omitted the sentence.

13. Which exact underlying causes of HT had the eight children with “combined underlying causes”?

Answer: Thanks for your recommendation. In our study, there are some patients presented with multiple systemic diseases, such as one patient had nephrotic syndrome and MR/DCM. But we classified the patients depending on the major problem that induced secondary hypertension. We have omitted the sentence to avoid the any misunderstanding.

14. Give percentages together with the absolute n-values.

Answer: Thanks for your recommendation. We have corrected it in our revised manuscript.

15. BMI must be given in SDS values and NOT in absolute values as it changes with age (in text and in tables).

Answer: Thanks for your recommendation. In our revised manuscript, we have presented the BMI (Z-score) in the table 2.
16. **SBP and DBP must be given in SDS values or as BP index and NOT in absolute values as they change with age (in text and in tables).**

Answer: Thanks for your recommendation. In our revised manuscript, we have presented the SBP/DBP (Z-score) in the **table 2**.

17. **Give exact numbers of antihypertensive drugs used, exact names of the drugs.**

Answer: Thanks for your recommendation. We have described these medications in our manuscript,

On page 15 in line 4:

**Nine patients received multi-antihypertensive agents. Long-term-acting amlodipine besylate** was used in seven patients; atenolol in nine patients; captopril in six patients; nifedipine in four patients; carvedilol, inderol and labetalol were used separately in three cases; and pentoxifylline, servidipine, lisinopril, and nicametate were each used once. Besides, none of them received antihypertensive medication before arriving pediatric ED.

18. **Give exact numbers of BP during the hours or days of hospitalisation instead of saying “BP decreased slowly”.**

Answer: Thanks for your recommendation. In our revised manuscript, we have described these statements more detailed. (On page 9 in line 12)

**Patients with hypertensive encephalopathy:**

19. **Give exact numbers of BP instead of saying “both much higher BP”**.

Answer: Thanks for your recommendation. In our revised manuscript, we have described these statements more detailed. (On page 14 in line 7)

20. **How fast the coma recovered?**

Answer: All coma patietns recovered within 30mins, but their blood pressure under well control about 2-3 days of hospitalization

21. **How was the BP during recovery?**
Answer: All coma patients recovered within 30 mins, but their blood pressure under well control about 2-3 days of hospitalization

22. *Give exact primary oncologic diseases, give the exact numbers.*

Answer: Thanks for your recommendation. In our revised manuscript, we have described these statements more detailed in the text.

On page 14 in line 13:

Oncologic causes were the major factors in these patients with hypertensive encephalopathy, and one was induced from pheochromcytoma with neurofibromatosis and one from paraganglioneuroma.

*Case distribution analysis and treatment:*

23. *The authors state that “there was no any sequelae” – how the sequelae were defined? and how they were excluded?*

Answer: Thanks for your recommendation. The sequelae here are those derived from acute end organ damages of hypertensive emergency, but chronic sequelae from hypertension. There was no patient presenting any sequelae derived from acute end organ damages after the BP recovered.

On page 15 in line 7:

During the study period, there was not any mortality nor any sequelae, following end organ damages

24. *Did really only 9 of 55 patients with HTN crisis receive multi-antihypertensive agents?*

Answer: Yes, there were indeed 9 of 55 patients with HTN crisis received multi-antihypertensive agents.

*Discussion:*

25. *The sentence “Age is an indispensable factor for HTN crisis, ……….” is NOT correct and should be omitted.*

Answer: Thanks for your recommendation. In our revised manuscript, we have omitted the sentence.

26. *The sentence on BMI should be reworded acc. the results of BMI –SDS data*
statistics.

Answer: After switched to BMI (Z-score), they seemed have no correlation with age. So we omitted the BMI in the sentence.

27. Most children with stage 2 hypertension does NOT have symptomatic HTN crisis and therefore the sentence “We therefore believed the 99th percentile plus 5 mm Hg could be.....” should be omitted.

Answer: Thanks for your recommendation. But actually, all the hypertensive crisis patients were symptomatic, and most of them present with stage 2 hypertension.

28. There is no discussion on similar previously published studies on HTN crisis in children – this must be added and similarities, differences and controversies should be discussed.

Answer: Thanks for your recommendation. In our revised manuscript, we have tried to discuss more about the similarities, differences and controversies in the discussion section.

29. What is the novelty of this study in comparison to other previous studies?

Answer: Thanks for your recommendation. In this study, we focused on the first-attack hypertensive crisis in children, the patients without clear history of hypertension, and had been trying to search for any predictor related to severity of hypertensive crisis. Besides, we compared various parameters among different age group, and you can see except essential HTN, there is no significant trend with age increased.

Minor comments:

Results:

30. Give the results of different data also in percentages (i.e. n=8, x%).

Answer: Thanks for your recommendation. We have corrected it in our revised manuscript.

31. Give exact numbers of renal diseases and endocrine disease (n=.., x%).
Answer: Thanks for your recommendation. We have corrected it in our revised manuscript.

On page 12 in line 13:

32. Neurofibromatosis is not primarily oncological but genetic disease and hypertension in children with NF is usually caused by renal artery stenosis. What was the cause of hypertension in children with NF?

Answer: Thanks for your recommendation. The patients with neurofibromatosis was also associated with pheochromcytoma. In our revised manuscript, we have corrected the omit.

On page 13 in line 4:

The oncological disorders were neurofibromatosis with pheochromcytoma and paraganglioneuroma, that also derived from endocrine diseases.

33. The recurrence rate of HT crisis is high. When the HT crisis recurred in the patients?

Answer: Thanks for your recommendation. When the HTN recurred depended on the underlying cuases, such as the essentail HTN patients recurred about 3-4 years later, but pheochromocytoma may recur several times within the same year.

34. Add (see Table 1) behind the words “...essential HTN had a significant correlation with age”

Answer: Thanks for your recommendation. We have corrected it in our revised manuscript.

Patients with hypertensive encephalopathy:

35. How long was the “study period”? (with recurrent HTN crisis)

Answer: Thanks for your recommendation. In our revised manuscript, we have added the detailed period after the sentence. On page 14 in line 15:

Two of them had recurrent hypertensive crisis episodes during the study period, January 2000 to January 2008.
36. Was MRI done in ALL children with HTN encephalopathy?

   Answer: Thanks for your recommendation. Actually, not all the patients with HTN encephalopathy received MRI, but others had received brain CT.

37. Were the MRI findings compatible with the diagnosis of PRES?

   Answer: Yes, the MRU finding compatible with the diagnosis of PRES

38. The exact values of lactate, NAA, choline and creatine levels are NOT given in Table 3.

   Answer: Thanks for your recommendation. But the MRI image was performed five years ago, the detailed original data was missed. So we could only describe the report of the image. Should we attached the MRS image?

   Discussion:

39. What does it mean “..of high P”?

   Answer: Thanks for your recommendation. In our revised manuscript, we have corrected the omit
   On page 16 in line 6:
   ...of high BP.

40. Neurofibromatosis is in children usually NOT catecholamine producing tumor – should be changed.

   Answer: Thanks for your recommendation. The patients with neurofibromatosis was associated with pheochromocytoma. In our revised manuscript, we have corrected the omit.
   On page 7 in line 1:
   Catecholamine producing tumors, such as pheocromocytoma and paraganglioneuroma
Dear reviewer #2:

Enclosed is our revised manuscript (First-attack Pediatric Hypertensive Crises presenting to the Pediatric Emergency Department). We appreciate the constructive comments of your review and have revised the manuscript. Below are our replies to the reviewers:

Itemized comments

1. **Whilst it is an interesting topic worth publication, the study was performed retrospectively on a small number of patients; this should therefore be mentioned in the manuscript.**

   Answer: Thx for your precise suggestions for improving our manuscript. We have added the following sentence in the revised manuscript.
   
   On page 5 in line 4:
   
   Therefore, we conducted a retrospective study on a small numbers of patients during 2000 to 2008.

2. **Another major point is that the blood pressure measurements are probably done by multiple observers over a long period of time, which should be discussed in the manuscript.**

   Answer: Thanks for your recommendation. We have added the following sentence in the revised manuscript.
   
   On page 7 in line 19:
   
   During the study period, the blood pressure measurements were done by multiple observers, all receiving well training and qualified nurses.

3. **In addition, BP index or BP Z-scores should be reported in addition to absolute BP data**

   Answer: Thanks for your recommendation. We have added the SBP Z-score and DBP Z-score in the table 2.

Minor points for revision

Abstract:

4. **The sentence “Primary clinicians should take attention to the pediatric patients..” should be reworded. Suggestion: “Primary clinicians should pay attention to their...**
pediatric patients...

Answer: Thx for your precise suggestions for improving our manuscript. We have corrected it in the revised manuscript.

5. It should be stated that it is a retrospective study.

Answer: Thanks for your recommendation. We have added the following sentence in the revised manuscript.

On page 2 in line 7:
We conducted a retrospective study during 2000 to 2008 for pediatric patients aged 18 and younger with a diagnosis of hypertensive crisis at the ED.

6. There is a spelling error in the abstract conclusion, please correct.

Answer: Thx for your precise suggestions for improving our manuscript. We have corrected it in the revised manuscript.

Introduction:
7. The main objective of the study is not clearly formulated. What do the authors mean by “clinically analyze”?

Answer: Thanks for your recommendation. We have corrected the sentence in the revised manuscript.

On page in line :
The main objective is to study the clinical features, etiology and treatment of children with first attacks of hypertensive crisis arriving at the pediatric emergency department (ED), and to analyzed predictors for the severity of hypertensive crisis in children.

Methods:
8. Exclusion criteria where the presence of a medical condition is incompatible with the definition of hypertension? Do the authors mean children who are not hypertensive, as per the definition of hypertension in children and adolescents?

Answer: Thanks for your recommendation. The change of definition of pediatric hypertension have been made since 2004. Some patients was diagnosed as hypertension before 2004, but actually presented with BP below the 95th percentile. We have corrected the sentence in the revised manuscript to avoid any
misunderstanding.

On page 6 in line 5:

We excluded the pediatric patients as below: the actual BP below the 95th percentile of BP, the final diagnosis of transient hypertension, asymptomatic hypertensive patients, and incomplete data; including inadequate body height or weight data, and no repeated BP measurement data.

9. End organ damages were defined as renal impairment, myocardial, renal, hepatic, hematologic and neurologic manifestation, all derived from HTN. What exactly was measured to assess the end organ damage?

Answer: Thanks for your recommendation. We have corrected the sentence in the revised manuscript.

On page 9 in line 9:

Abnormal finding including abnormal electrocardiography finding, elevated renal function, elevated liver function test, and any neurologic manifestations, such as headache, altered consciousness, dizziness.

Methods:

10. The sentence, “Total 112 patients presented to our pediatric ED with the primary and secondary diagnosis of hypertension”, should be reworded as: A total of 112 patients presented to our pediatric ED with the diagnosis of primary and secondary hypertension”.

Answer: Thanks for your recommendation. We have corrected the sentence in the revised manuscript.

11. What do the authors mean by the “rule of thumb” in the following sentence?

Answer: Thanks for your recommendation. The rule of thumb here generally meant 120/80mmHg. We have corrected the sentence in the revised manuscript to avoid any misunderstanding.

On page in line:

If the systolic BP (SBP) or diastolic BP (DBP) was higher than 120/80 mmHg, it was re-measured from both hands and legs.22

12. “If the systolic BP (SBP) or diastolic BP (DBP) was higher than the “rule of thumb” for the determination of BP thresholds for the diagnosis of arterial
hypertension in children and adolescents, it was re-measured from other limbs.

What threshold values were used for BP measurements of the limbs?

Answer: Thanks for your recommendation. The threshold values used for BP measurement of the limbs was still based on the definition of HTN on 2004, that the BP level above 95th percentile is hypertension. After remeasurement, the BP level recorded from left hand would be still preferred, if the BP levels from other limbs are still above 120/80mmHg.

13. If the BP was measured repeatedly in each patient, what values were taken from the analysis? The highest BP value? An average BP value? How many BP values per patient were available and which ones were then used for comparison with the normative values/BP threshold?

Answer: Thanks for your recommendation. The threshold values used for BP measurement of the limbs was still based on the definition of HTN on 2004, that the BP level above 95th percentile is hypertension. After remeasurement, the BP level recorded from left hand would be still preferred, if the BP levels from other limbs are still above 120/80mmHg.

14. What BP standards were actually used for the definition of hypertension? What was the reason to not use the normative values from the Fourth Report (Pediatrics 2004;114:555)?

Answer: Thanks for your recommendation. The definition of hypertension from the Fourth report was the BP standards for this study. But the report didn’t include the BP standards for children younger than 1 year of age. So we adopted the Dr Kent AL’s infant BP standard to diagnosed infant hypertension.

15. The sentence, “Asymptomatic HTN were defined by us for patients with BP higher than the 95th percentile in three times but presenting with unrelated symptoms to hypertension before and after arriving pediatric ED”, should be reworded.

Answer: Thanks for your recommendation. The patients diagnosed as asymptomatic HTN was excluded initially. So we have omitted the sentence to avoid any misunderstanding.
16. The legend to Table 1 should be changed as the term correlation is not correct; it is a description of results obtained in various age categories. The same applies for the legend to Table 2.

   Answer: Thanks for your recommendation. We have corrected the sentence in the revised manuscript.

17. Data on Figure 2 is already presented in the tables, therefore Fig 2 can be deleted.

   Answer: Thanks for your recommendation. We have corrected the sentence in the revised manuscript.

Discussion

18. The discussion contains several non-English expressions; please correct.

   Answer: Thanks for your recommendation. We have corrected the paragraph in the revised manuscript.

19. The discussion should state the limitations of the study such as retrospective study, small sample size, BP taken over a span of an 8 year period etc. Was the BP measured with the same BP device over an 8 year period?

   Answer: Thanks for your recommendation. We have corrected the paragraph in the revised manuscript. Besides, there were about four devices having been used for BP measurement during 2000 to 2008.

   On page in line: The study has certain limitations that need to be taken into account: retrospective study in a small sample size, BP taken over a span of an 8 year period, and the noncooperation in younger patients. Although we reviewed the patients for eight years, there were still only 55 patients due to the incidence of hypertensive crisis is relatively low. The skillful BP measurement, history taking and careful physical examination were all important for approaching the hypertensive crisis patients. Most hypertensive children were usually undertreated because of the nonspecific symptoms. So we expected there would be further more researchs in the field.