Peer Review File

Review Comments

It is a multicenter retrospective cohort study looking at the association between proton pump inhibitors and pediatric AKI. This manuscript needed revision to complete.

Major comments:

1. The results showed that the effects of PPI appeared to be independent of drug subtypes, methods of administration, and among children of different age range and gender. Notably, children with CKD or needing intensive care were more susceptible to PPI-related AKI than those without. But it's mentioned in the discussion on page 17, in subgroup analyses stratified by age, gender, CKD, ICU, operation and use of NSAIDs, the association between PPI use and risk of HA-AKI were consistent with the overall study population. There is a contradiction between these two statements. Please explain.

Reply 1: We are sorry for the confusion about the aforementioned sentence "… the association between PPI use and risk of HA-AKI were consistent with the overall study population". What we mean is that the association between PPI use and risk of HA-AKI was consistently conserved in all the subgroups examined, even though the effect size may be larger in some subgroups such as children with CKD or needing intensive care.

Changes in the text: To clarify, we have revised the sentence on page 15 lines 312-315 as the following. "*Second, the association between PPI use and risk of HA-AKI was consistently observed in all subgroups stratified by age, gender, CKD, need for intensive care, receiving operation and use of NSAIDs.*"

2. It's a study about children, why only those aged from 1 month to 18 years old were selected? Why not include people less than 1 month old?

Reply 2: Currently, there is no consensus on defining AKI in neonates. The level SCr of the newborns at birth is same as the mothers, with an average of about 50-60 umol/L. However, the SCr level in neonates drops quickly to about 20 umol/L in 2-4 weeks after birth. Therefore, we excluded neonates in our study.

References:

1. Libório AB, Branco KM, Torres de Melo Bezerra C. Acute kidney injury in neonates: from urine output to new biomarkers. Biomed Res Int. 2014;2014:601568. doi:10.1155/2014/601568

2. Mian AN, Guillet R, Ruck L, Wang H, Schwartz GJ. Acute Kidney Injury in Premature, Very Low-Birth-Weight Infants. J Pediatr Intensive Care. 2016;5(2):69-78. doi:10.1055/s-0035-1564797

3. Age, gender, comorbidities, baseline SCr and other factors were adjusted. Please explain the specific adjustment method.

Reply 3: In the regression models, natural spline terms (df=4) were used for the adjustment of age, baseline SCr and time from admission. Other variables, including gender, need for intensive care, and each hospital of admission, division of admission, comorbidity (gastroesophageal reflux disease, gastrointestinal tract bleeding, other acid-suppression related diseases, respiratory infection, urinary tract infection, congenital urinary system malformation,

congenital heart disease, glomerulonephritis, malignant solid tumor, hematological malignancy, diarrhea, epilepsy, trauma), operation procedure (gastrointestinal operation, cardiac operation, respiratory operation, neurosurgical operation, orthopedic operation, urinary system operation, other operation), nephrotoxic drug (NSAIDs, chemotherapy agents, contrast medium, corticosteroids, ACEI, ARB, thiazide diuretic, loop diuretic, nephrotoxic antibiotics) listed in table 1, were coded as "yes/no" categorical variables.

Changes in the text: Page 9, lines 194-195: "*In the regression models, natural spline terms (df=4) were used for the adjustment of quantitative variables such as age, baseline SCr and time from admission.*"

Minor comments:

1. There are a lot of data in this paper, especially some percentages. Please check the correctness of these data again. For example, 1,666 (4.2%) of 42,232 people use H2RA, which is 3.9%, not 4.2%.

Reply 1: Thank you for pointing out this error. We have double-checked the entire manuscript and revised the number accordingly.

Changes in the text: Page 3, line 54: "*1,760 (4.2%) used histamine 2 receptor antagonist (H2RA).*"

2. English language should be polished; sentence pattern needs to be adjusted. E.g. i) the correctness of the words ("point t, before t, after t" on page 9), ii) first abbreviation must be completed full names (e.g. page 12 pROCK).

Reply 2: We have revised the manuscript as suggested.

Changes in the text: Page 7, lines 135-138: "*Briefly, at any time point denoted by t , a baseline creatinine was dynamically defined as the mean creatinine level within the last 90 days before t , and each of the available creatinine data within 7 days after t was compared with this baseline.*"