Author’s response to reviews

Title: Clinical characteristics of adrenal crisis in adult population with and without predisposing chronic adrenal insufficiency: a retrospective cohort study

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Author’s response to reviews:

We wish to express our strong appreciation to the Reviewers for their insightful comments on our paper. We feel the comments have helped us to significantly improve the paper.

Reviewer reports:

Miguel Debobo (Reviewer 1): In this paper by Iwasaku et al investigators attempt to investigate the reasons for admission to hospital of patients with adrenal crises looking at various predisposing factors. The paper lacks clarity and does not focus on the main objectives of the study. It is hard to follow the authors train of thought as they go from one subject to another. The paper needs to be proof read by an editor experienced in writing in English.

Response

We appreciate the reviewer’s comment on this point. As a result, we have made the writing more concise and deleted unnecessary text in the “Introduction” and “Discussion”. We have had the manuscript edited by an experienced scientific editor, who has improved the grammar and stylistic expression of the paper.

1. In line 80 what does "to describe candidates as precipitating conditions for AC and the use of GC therapy" mean?
Response:

I intended to describe risk factors for AC. Based on your question, we made the following change. (Introduction, line 95, page 6):

"to describe candidates as precipitating conditions for AC and the use of GC therapy."


to

“to describe candidate risk factors such as comorbidity and GC therapy.”

2. Case ascertainment for the "other" group might not be so accurate and it is not clear how this group of patients were diagnosed with adrenal crises. Could this group have patients suffering from diseases treated with glucocorticoids such as inflammatory conditions e.g asthma, inflammatory bowel disease who are on regular steroids and are more likely to be admitted to hospital with acute exacerbations of their condition as opposed to adrenal crises?

Response:

Yes, the “Others” group could include such patients. According to your comment, we checked the admissions within 1 year before the index admission. We also compared the characteristics between patients who were and were not admitted while under glucocorticoid-related medication and were and were not admitted within 30 days after glucocorticoid cessation. In “Methods”, “Results”, and “Supplementary Materials”, we added further explanations as follows. (Methods, lines 176-181, page 10-11; Results, lines 313-324, page 21; Table S9-11)

Methods

“The category of “Others” included various predisposing diseases, examples of which are undiagnosed chronic AI, relative AI, and drug-induced AI. But, provision of criteria is difficult for these specific predisposing conditions. To explore these latent conditions in “Others”, we compared clinical characteristics on admission with or without the following: 1) prior admission (within 1 year before AC); 2) GC medication (including drugs interacting with GC), and 3) GC cessation (within 30 days before AC).”

Results

Characteristics of patients in the “Others” group
“There was a higher proportion of patients in the “Others” group than in the Primary AI and Central AI groups with admissions within 1 year before AC (Primary AI: 17.4%, 4/23; Central AI: 21.3%, 29/136; Others: 44.1%, 152/345). We compared characteristics of patients in “Others” according to the presence of the following groups: 1) prior admission (Table S9); 2) GC medication (Table S10), and 3) GC cessation (Table S11). Patient characteristics were similar among those in the three groups: cancer was a major comorbidity and hormone testing before AC had been performed widely. Prior admission within 1 year before AC was prevalent in patients in either GC medication group or GC cessation group (65.0% or 90.3%, respectively). One key difference between these two groups was that the patients in GC cessation group did not include any patient with an autoimmune disease as a comorbidity.”

3. Line 147 I guess should be changed to the presence of a disease considered to be the cause for primary AI

Response: We made the following revision (Methods, line 166, page 10).

“1) the presence of a disease considered to be a risk factor for primary AI”

to

“1) the presence of a disease considered to be the cause for primary AI”

4. What are endocrine stimulation test and adrenal cortex stimulation test referring to? Is this the Short Synacthen test?

Response: In accordance with the reviewer’s comment, we added following explanation in the footnote of Table 4.

“Endocrine stimulation test consists of hormone dynamic testing of the following: anterior pituitary (growth hormone, gonadotropin, thyroid stimulating hormone, prolactin, adrenocorticotropic hormone), posterior pituitary (antidiuretic hormone), thyroid, parathyroid, and gonad (testosterone, estradiol). Endocrine tests of adrenocorticotropic hormone included insulin tolerance test, metyrapone test, dexamethasone suppression test, and corticotropin-releasing hormone stimulation test. In this study, we counted results of the adrenal cortex stimulation test apart from those for endocrine stimulation tests. The adrenal stimulation tests evaluates adrenal cortex function, which is related to glucocorticoid or mineralocorticoid, for example, the adrenocorticotropic hormone stimulation test.”
5. Line 230 what does one mean by commenting that the most common cause for patient with primary ai is ai? Is this adrenal crisis?

Response:

Yes, AI should have been AC. We changed this and also added a footnote in Table 2 for clarification. (Results, lines 265, page 17; Table 2)

“For patients with primary AI, the most frequent indication for hospitalization was AI (26.1%).”

to

“for patients with primary AI, the most frequent indication for hospitalization was AC (26.1%).”

6. It would be interesting to know in the text what the measured cortisol levels were for patients diagnosed with adrenal crisis

Response:

We agree that additional information on the measured hormone levels would be valuable but we could not obtain laboratory values such as serum cortisol levels. We cited this as a limitation in the “Discussion” as follows: “Second, we could not evaluate laboratory values such as serum cortisol levels.” (Discussion line 446, page 28)

Mi-Kyung Kim (Reviewer 2): Review

Adrenal crisis is life threatening disease but there is lack of data. Therefore, this manuscript is valuable to find characteristics of adrenal crisis. However, there are some questions about the study

1. Table S1

(1) Table S1 showed disease list based on ICD-10.

Could you check iatrogenic Cushing syndrome (E24.2)?

Response:

The original selection criteria specified in the study protocol did not include iatrogenic Cushing syndrome (E24.2) and, unfortunately, a dataset for reanalysis is not available. All we can do is to check iatrogenic Cushing syndrome (E24.2) in the original data source (population: 0.6 million).
We found 6 patients labeled as having iatrogenic Cushing syndrome but after careful consideration only one case corresponded with AC after considering therapeutic glucocorticoid administration and admissions.

2. Authors divided 3 groups; primary, secondary and others.

Authors defined "others" as adrenal insufficiency with various pathophysiologic background. However, it is not clear. According to reference 1, drug induced adrenal insufficiency is classified as tertiary (hypothalamic). Because of lack of confirmation test between pituitary or hypothalamic origin, it could be better to divide primary/secondary, namely primary/central. If authors used primary/secondary (hypothalamic-pituitary) and others, do authors classify drug-induced adrenal insufficiency as other could be one of the list of secondary adrenal insufficiency. I think this classification is not usual. Therefore, based on reference 1, 16, authors need to define "others" more clearly.

Response:

In accordance with the reviewer’s comment, we converted primary/secondary into primary/central. We think that it would be ideal to define glucocorticoid withdrawal syndrome clearly; however, information in the claim database is insufficient for this. Therefore, in the “Others” group, we compared patient characteristics according to whether or not there were admissions under glucocorticoid-related medications. In “Methods”, “Results”, and “Supplementary Materials”, we added further explanations.

(Methods, lines 176-181, page 10-11; Results, lines 313-324, page 21; Table S10)

Methods

“The category of “Others” included various predisposing diseases, examples of which are undiagnosed chronic AI, relative AI, and drug-induced AI. But, provision of criteria is difficult for these specific predisposing conditions. To explore these latent conditions in “Others”, we compared clinical characteristics on admission with or without the following: 1) prior admission (within 1 year before AC); 2) GC medication (including drugs interacting with GC), and 3) GC cessation (within 30 days before AC).”

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3. Comorbidity in table 2 is accompanied disease at admission. It could be a direct or indirect cause of adrenal crisis. As authors mentioned, discontinuation of drug is one of the common cause of adrenal crisis. It is helpful to check direct causes of adrenal crisis at index date for prevention of adrenal crisis.

Response:

Based on your suggestion, we made an additional analysis of adrenal crisis within 30 days after GC cessation. In “Methods”, “Results”, and “Supplementary Materials”, we added further explanations. (Methods, lines 176-181, page 10-11; Results, lines 313-324, page 21; Table S11)

Methods

“The category of “Others” included various predisposing diseases, examples of which are undiagnosed chronic AI, relative AI, and drug-induced AI. But, provision of criteria is difficult for these specific predisposing conditions. To explore these latent conditions in “Others”, we compared clinical characteristics on admission with or without the following: 1) prior admission (within 1 year before AC); 2) GC medication (including drugs interacting with GC), and 3) GC cessation (within 30 days before AC).”

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