Reviewer's report

Title: Clinical characterization of patients with primary aldosteronism plus subclinical Cushing's syndrome

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Reviewer: Warrick Inder

Reviewer's report:

Yasuda et al review their experience in patients with primary aldosteronism, subclinical Cushing's and both conditions occurring concurrently which they have termed PASCS.

Specific comments:

1. The authors state that they began with 187 patients, 133 with PA and 54 with SCS but neither was "definitely diagnosed" in 115. Can the authors briefly expand on this and explain how these 115 patients failed to meet the diagnostic criteria?

2. The diagnosis of subclinical Cushing's syndrome is controversial and international bodies can't even come up with a consensus regarding the name! It appears the authors have diagnosed SCS only in patients with a post 1mg dexamethasone cortisol of greater than or equal to 5 mcg/dL and not the other SCS criteria as outlined in the citation from Yanase et al (ref 6). Is this correct? The fact that ACTH was not lower in the SCS group than the PA group makes me question how many of the SCS or PASCS patients truly had autonomous hypercortisolism. The authors should take into account the seminal paper by Lee et al Clin Endocrinol 2017; 86; 10-18 and include ACTH and DHEAS in their diagnostic criteria. A failed DST with cortisol of more than 5 mcg/dL without evidence of low ACTH or DHEAS might be due to chronic stress or even ACTH-dependent hypercortisolism rather than autonomous cortisol secretion from an adrenal adenoma. My suggestion is that the diagnostic criteria for SCS need further explaining and that re-analysing the data to limit the diagnosis of SCS to the cases with low ACTH or DHEAS would tighten the manuscript considerably.

3. The difference in adenoma size between the PA patients and the other two groups is of interest. The SCS with a diameter of 7mm is a major outlier and I suspect probably does not have autonomous cortisol secretion from this lesion, as defined using Lee's criteria.

4. Overall the findings are of interest, particularly that the PASCS group have the hypokalaemia of the PA patients and the hyperglycemia and tumor size of the SCS patients. Could the authors analyse what the probability/odds ratio and sensitivity/specificity is of a PA patient having co-existing SCS based on tumor size, and what the cut point would be. Based on the appearance of figure 1, all patients with an adenoma size of greater than approx. 2.3cm are likely to have PASCS rather than PA alone.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

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