




## Letter to the editor on “Ablation versus laparoscopic adrenalectomy for the treatment of aldosterone-producing adenoma: a meta-analysis”

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Received: 4 February 2021 / Revised: 4 February 2021 / Accepted: 11 February 2021

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To the editor,

Chen et al. [1] meta-analyzed the studies comparing radiofrequency ablation (RFA) with laparoscopic adrenalectomy (LA), which is currently held to be the gold standard for the surgical treatment of patients with primary aldosteronism (PA) due to unilateral aldosterone-producing adenoma (APA). They could include only five small non-randomized retrospective studies [2–6], and, moreover, their meta-analysis was affected by several methodological flaws and mistakes that, on the whole, question the validity of its results and the strength of its conclusions.

First, prerequisites for including studies in a meta-analysis are a thorough check of their quality and exclusion of duplicated cases. The study by Chen et al. [1] fell short on both these items. They could not include any prospective randomized trial and the quality assessment score used by the Authors [7] revealed that all studies included are high quality, but the Newcastle–Ottawa score (NOS)

is not appropriate as it is designed for cohort-studies and case–control studies. Moreover, of the five meta-analyzed studies two were by Liu et al. [3, 4] and included duplicated series of patients treated with RFA.

Second, according to guidelines [8, 9], unilateral PA due to an aldosterone-producing adenoma should be diagnosed based on an adrenal vein sampling (AVS) showing lateralized aldosterone secretion. Oddly enough, the AVS was routinely performed in just one of the five meta-analyzed studies, [2] and therefore, the presence of unilateral and bilateral form of hyperaldosteronism could not be ascertained. Likely this worsened the outcome of adrenal ablation in both treatment groups thus blunting differences between RFA and LA.

Third, on a biological plausibility ground, one cannot imagine any reasons why in lowering blood pressure (BP) a presumably total adrenal ablation achieved with RFA should surpass the certainly total adrenal ablation achieved with LA. Additionally, for the analysis of the BP outcome the Authors compared studies that reported the highest BP value measured [4] and studies that provided the mean BP values [2, 5, 6]. Moreover, the study by Liu et al. [4] considered the highest BP values at baseline and the mean BP values at follow-up, thus clearly overestimating the BP lowering effect of treatment and affecting the meta-analysis conclusions. By repeating the meta-analysis after exclusion of this study, it can be found that the reduction of systolic BP (SBP) and diastolic BP (DBP) was less different between the RFA group and the LA group.

Fourth, while being limited methodologically by the fact that they rely on summary data and not on individual data, meta-analyses require a precise knowledge of the measures of spread of the variables to be meta-analyzed. Of note, in four of the five studies included in the meta-analysis, the standard deviation (SD) was not provided [2–5]. Regrettably, no information was provided on how the SDs were calculated for the mean change of key variables as SBP, DBP, and serum potassium levels (K<sup>+</sup>). Furthermore, in the four

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This comment refers to the article available online at <https://doi.org/10.1007/s00261-020-02887-8>.

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articles that should have been included [2, 4–6], the efficacy analysis was based on data recorded at different follow-up times with no standardization, which makes results difficult to compare, as the short-term changes in BP values could have been influenced by post-operative stress, pain, blood loss, and other peri-procedural complications. Moreover, it would seem that the Authors ‘picked cherries’ in their analysis of the pre- and post-treatment  $K^+$  levels as they did not include the study by Yang et al. [5] even though the original article reported such data.

Fifth, the meta-analyzed studies used different operative techniques: Yang et al. [5] used the retroperitoneoscopic approach for both the LA and the RFA, whilst the other Authors [2–4, 6] used a transperitoneal approach for LA and a CT-guided RFA. Moreover, Yang et al. [5] exploited performance of partial adrenalectomy, while total LA was described in the other four studies. While partial adrenalectomy should be guided by superselective AVS in order to identify the culprit nodule (-s) [10], this could have influenced the meta-analysis results in terms of safety (minor and major complications), duration of the procedures, and also clinical outcomes.

Sixth, in Yang et al. [5], the LA and RFA group differed in the baseline APA dimension at baseline ( $2.67 \pm 0.54$  cm for LA and  $1.81 \pm 0.59$  cm for RFA;  $p < 0.05$ ), indicating that patients with smaller tumors were assigned to RFA, which introduced an obvious important selection bias. To partially overcome these problems, a meta-regression analysis should have been undertaken, but regrettably it was not done.

Finally, although the Authors stated that percutaneous ablation offers a number of advantages over LA, including no requirement for general anesthesia, this was by no means supported by their own findings as in the majority of the studies that they meta-analyzed RFA was performed under general anesthesia [2, 5, 6].

In summary, given the epidemics of primary aldosteronism, pursuing strategies of adrenal ablation that are less invasive, simpler, cheaper and more widely available than LA is certainly a worth effort. However, to support replacement of LA with RFA for the treatment of unilateral PA, far more solid data than those coming from this meta-analysis,

which can be provided by carefully designed randomized clinical trials, are needed.

**Funding** The study was funded by FORICA (The Foundation for advanced Research In Hypertension and Cardiovascular diseases), University of Padua, and The International PhD Program in Arterial Hypertension and Vascular Biology.

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